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<p>(54) Title: TRYPSIN AND THROMBIN INHIBITORS</p>		
<p>(57) Abstract</p> <p>The present invention provides a compound of general formula (I), in which Ar is a substituted or unsubstituted aryl or heterocyclic residue; Aa is an amino acid residue usually of L configuration and (a) is a residue of formula (IV) or formula (V), wherein X is hydrogen or a C₁-C₅ alkyl group; Y is a) an SO₃H, PO(OR¹⁴)₂, OH, SH, NR¹⁵R¹⁶, or halogen group or is b) a residue -(C_qH_{2q})-Q wherein Q is H, COR¹⁴, CO₂R¹⁴, CONR¹⁵R¹⁶, SO₃H, OR¹⁴, OCOR¹⁴, PO(OR¹⁴)₂, NR¹⁵R¹⁶, SR¹⁴ or Hal wherein R¹⁴, R¹⁵ and R¹⁶ are hydrogen, C₁-C₅ alkyl, C₅-C₈ cycloalkyl or C₇-C₁₁ aralkyl or R¹⁵ and R¹⁶ together with the nitrogen atom to which they are bound form a 5 or 6 membered azacycloalkyl or oxazacycloalkyl, q is 0 or an integer from 1 to 8 and the residue C_qH_{2q} may be optionally substituted by OH or interrupted by oxygen, sulfur, oxycarbonyl O.CO, carbonyloxy CO.O, aminocarbonyl NHCO, sulfonamido, NHSO₂ or carboxamido CONH; or is c) a residue (C_wH_{2w+1-y-z})F_yOH_z in which w is an integer from 1 to 8, y is an integer from 1 to 17 and z is 0 or 1, or X and Y together are = O, Z is a direct bond, oxygen or nitrogen optionally substituted by X or Y, m = 2 to 4, n = 2 to 4 and m + n = 4 to 6, j = 0 to 2, k = 0 to 2 and j + k = 2 or 3, wherein X has its previous significance and Y is a residue (C_qH_{2q})-Q, wherein q and Q have their previous significance, and salts thereof, provided that when As is arginine, X and Y are not alkyl and when Q is COR¹⁴, q is an integer from 1 to 8.</p>		
<div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;"> $\text{ArSO}_2\text{Aa} \quad \text{N Het} \quad (I) \quad \text{N Het} \quad (a)$ </div> <div style="text-align: center;"> <p>(IV)</p> </div> <div style="text-align: center;"> <p>(V)</p> </div> </div>		

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TRYPSIN AND THROMBIN INHIBITORS

The present invention relates to new compounds which have activity as inhibitors of trypsin and thrombin.

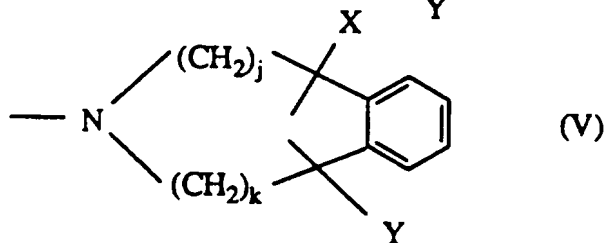
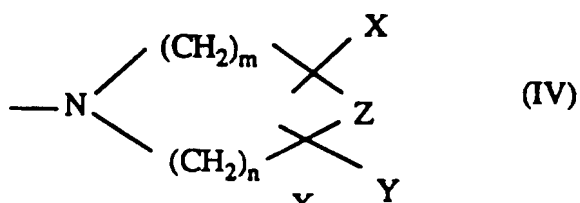
Accordingly the present invention provides a compound of the general formula I



in which Ar is a substituted or unsubstituted aryl or heterocyclic residue; Aa is an amino acid residue usually of L configuration and



is a residue of formula IV or formula V

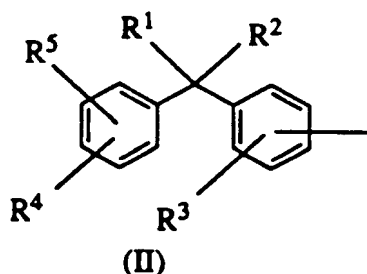


wherein X is hydrogen or a C₁-C₅ alkyl group, Y is a) a SO₃H, PO(OR¹⁴)₂, OH, SH, NR¹⁵R¹⁶, or halogen group or is b) a residue -(C_qH_{2q})-Q wherein Q is H, COR¹⁴, CO₂R¹⁴, CONR¹⁵R¹⁶, SO₃H, OR¹⁴, OCOR¹⁴, PO(OR¹⁴)₂, NR¹⁵R¹⁶, SR¹⁴ or Hal wherein R¹⁴, R¹⁵ and R¹⁶ are hydrogen, C₁-C₅ alkyl, C₅-C₈ cycloalkyl or C₇-C₁₁ aralkyl or R¹⁵ and R¹⁶ together with the nitrogen atom to which they are bound form a 5 or 6 membered azacycloalkyl or oxazacycloalkyl, q is 0 or an integer from 1 to 8 and the residue C_qH_{2q} may be optionally substituted by OH or interrupted by oxygen, sulfur, oxycarbonyl O.CO, carbonyloxy CO.O, aminocarbonyl NHCO, sulfonamido, NHSO₂ or carboxamido CONH; or is c) a residue (C_wH_{2w+1-y-z})F_yOH_z in which w is an integer from 1 to 8, y is an integer from 1 to 17 and z is 0 or 1, or X and Y together are = O, Z is a direct bond, oxygen or nitrogen optionally substituted by X or Y, m = 2 to 4, n = 2 to 4 and m+n = 4 to 6, j = 0 to 2, k = 0 to 2 and j+k = 2 or 3 wherein X has its previous significance

and Y is a residue $(C_qH_{2q})-Q$ wherein q and Q have their previous significance, and salts thereof, provided that when Aa is arginine X and Y are not alkyl and when Q is COR^{14} , q is an integer from 1 to 8.

Ar may be a substituted or unsubstituted phenyl residue, a substituted or unsubstituted naphthyl or partially hydrogenated naphthyl residue or a substituted or unsubstituted anthryl, phenanthryl or heterocyclic residue which may be partially hydrogenated.

When Ar is a substituted phenyl residue it may be substituted with one or more groups such as alkyl, alkoxy, hydroxy, alkyl thio, thio, halo, amino, substituted amino, nitro, cyano, aralkyl and the like. Particularly preferred are compounds of formula I wherein Ar is a residue of formula II

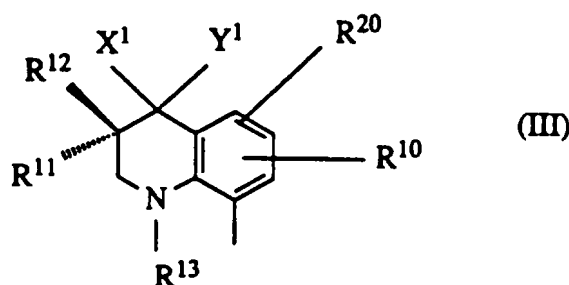


wherein R^1 and R^2 are C_1-C_5 alkyl or are linked to form a C_3-C_7 carbocyclic ring and R^3 , R^4 and R^5 are the same or different and are hydrogen, C_1-C_5 alkyl, OR^6 , SR^6 , halo, NR^7R^8 , NO_2 , CN , $CONR^7R^8$ or CO_2R^9 wherein R^6 is C_1-C_5 alkyl, C_3-C_8 cycloalkyl, C_7-C_{11} aralkyl and R^7 , R^8 , and R^9 are hydrogen, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, or C_7-C_{11} aralkyl, or R^7 and R^8 together with the nitrogen atom to which they are bound form a 5 or 6 membered azacycloalkyl or oxazacycloalkyl, and especially where R^3 is H or NH_2 and R^4 and R^5 are H or OCH_3 .

When Ar is a naphthyl or partially hydrogenated naphthyl residue it may be substituted for example by one or more residues R^3 which may be the same or different and where R^3 has its previous significance.

When Ar is an anthryl, phenanthryl or heterocyclic residue such as anthryl, phenanthryl, pyridyl, benzofuranyl, benzo(b)thienyl, quinolyl, isoquinolyl or the like which may be partially hydrogenated it may be substituted for example by one or more residues R^3 which may be the same or different and where R^3 has its previous significance.

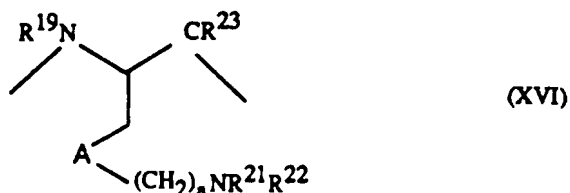
Particularly preferred are compounds of formula I wherein Ar is a quinolyl or partially hydrogenated quinolyl residue and especially where the residue Ar is a residue of formula III,



wherein R^{10} is hydrogen, halo e.g. bromo, chloro or fluoro, R^{20} is hydrogen or $(CH_2)_pD$ where p is 0 or an integer from 1 to 4 and D is C_1 - C_5 alkyl optionally interrupted by one or more oxygen atoms, C_1 - C_5 alkenyl, C_1 - C_5 alkoxy, a silane group, CHO, tetrazolyl, carboxyl, alkylcarboxyl, fluoro, cyano or $CHNOH$, R^{11} and R^{12} are hydrogen, a C_1 - C_5 alkyl which may be interrupted by one or more oxygen atoms, C_1 - C_5 alkenyl, alkoxyalkyl, hydroxyalkyl, alkylthioalkyl, alkylamino dialkylamino or trialkylamino, or together form either a methylene group or together with the carbon to which they are attached form a C_3 - C_7 carbocyclic ring, and R^{13} is hydrogen, C_1 - C_5 alkyl which may be interrupted by one or more oxygen atoms or C_7 - C_{11} aralkyl and X^1 and Y^1 are both H, one is H and one is OH or together are = O. Most preferred are those compounds of formula I wherein Ar is a residue of formula III wherein R^{10} is hydrogen or halo, R^{20} is C_1 - C_5 alkyl optionally interrupted by one or more oxygen atoms, carboxyalkyl or alkylcarboxyalkyl R^{11} and R^{12} are hydrogen or methyl and R^{13} is hydrogen.

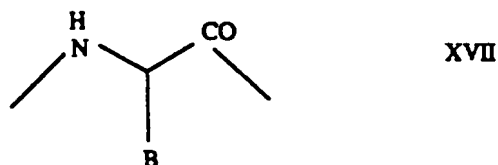
C_1 - C_5 Alkyl is, for example, a branched or unbranched alkyl such as ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or especially, methyl. C_3 - C_8 Cycloalkyl is, for example, cyclopentyl or cyclohexyl. Halogen is, for example, fluoro, chloro or bromo. C_7 - C_{11} Aralkyl is, for example, phenyl- C_1 - C_4 - alkyl such as 2-phenylethyl or, in particular, benzyl. 5 or 6 membered azacycloalkyl is, for example, pyrrolidyl or piperidyl while 5 or 6 membered oxazacycloalkyl is especially morpholyl.

Amino acid residue Aa may be a heteroaliphatic or heteroaromatic group having the formula XVI



where R^{19} is H or CH_3 , R^{23} is = O or = S, A is O, S, NH, SO_2 , CH_2S or CH_2 , R^{21} is H or CH_3 , R^{22} is H or CH_3 or when R^{21} is H may also be $C(NH_2) = NH$, and a is an integer from 1 to 4 or the formula XVII

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where B is a heterocyclic ring or heterocyclic methyl group, wherein the heterocyclic ring is optionally fused to a second ring which is a hydrocarbon or heterocyclic ring, and wherein the single or double ring system is optionally substituted by methyl, aminomethyl, phenyl or OH.

It should be noted that the carbon atom next to the N atom in formulae XVI and XVII may give rise to stereoisomers. The present invention includes the individual stereoisomers as well as mixtures. Preferably the compounds have the L configuration.

Compounds of formula I where

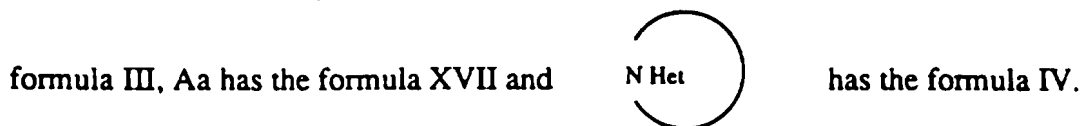


represents a piperidine group of formula IV are preferred. More preferably the piperidine ring is substituted by an ethyl group or a fluorethyl group.

One preferred group of compounds of formula I above are those where Ar has the formula III,



Another preferred group of compounds of formula I above are those where Ar has the

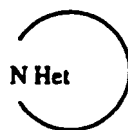


The N^α-arylsulfonyl-aminoacyl amides of formula I and the salts thereof of this invention are inhibitors of high specific activity in mammals including humans against thrombin and therefore these compounds are useful in the determination of thrombin in blood as diagnostic reagents, and/or for the medical treatment or prevention of thrombosis.

The compounds of formula I may be made by various processes as outlined in Methods A to

E of the Synthetic Schemes below. In these schemes below, A represents ArSO_2 , B

represents the aminoacid Aa and C represents



Synthetic Schemes

Method A: (C-B-C-A-B-C)

Base + N-protected aminoacid

↓ coupling

N-protected aminoacyl-base

↓ deprotection

aminoacyl-base

↓ i) coupling

↓ ii) deprotection (if needed)

Arylsulfonyl-aminoacyl-base

Method B: (B-A-B-A-B-C)

Arylsulfonyl chloride + aminoacid (derivative)

↓ coupling

Arylsulfonyl-aminoacid (derivative)

↓ deprotection (if needed)

Arylsulfonyl-aminoacid

↓ i) coupling

↓ ii) deprotection (if needed)

Arylsulfonyl-aminoacyl-base

Method C

Arylsulfonyl(l)-aminoacyl-base (by method A or B)

↓ i) modification or aryl group

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↓ ii) deprotection (if needed)

Arylsulfonyl(2)-aminoacyl-base

Method D

Arylsulfonyl-aminoacyl(1)-base (by method A or B)

↓ i) modification of amino acid

↓ ii) deprotection (if needed)

Arylsulfonyl-aminoacyl(2)-base

Method E

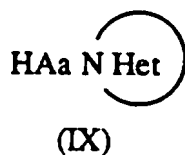
Arylsulfonyl-aminoacyl-base(1) (by method A or B)

↓ i) modification of base

↓ ii) deprotection (if needed)

Arylsulfonyl-aminoacyl-base(2)

In a first process compounds of formula I are prepared by reaction of aminoacyl amides of formula IX,



wherein Aa and



have their previous significance with an arylsulfonic acid derivative of formula VIII

ArSO_2W (VIII)

where W is OH or preferably an arylsulfonyl halide VIII where W is halogen especially Cl or Br and where the compounds of formula IX and VIII may be optionally protected and/or where the residue ArSO_2 in compounds of formula I comprises a partially hydrogenated

aromatic or heterocyclic system the compounds of formula VIII may contain hydrogenatable double bonds. The reaction of compounds of formula IX with arylsulfonyl derivatives VIII is carried out for instance under conditions known for introducing arylsulfonyl groups onto amino substituted compounds. In the above formulae, protected species are typically protected on the α -amino group, by benzyloxycarbonyl or t-butoxycarbonyl.

For instance compounds of formula I may be prepared by the condensation of an aminoacyl amide (IX) with a substantially equimolar amount of an arylsulfonyl halide VIII, preferably a chloride, to give a protected intermediate which yields the product I on deprotection. The condensation reaction is generally effected in a suitable inert solvent in the presence of an excess of a base, such as an organic base e.g. triethylamine, di-isopropylethylamine, pyridine, N-methyl or N-ethyl morpholine or a solution of an inorganic base e.g. sodium hydroxide or potassium carbonate, at a temperature of 0°C to the boiling temperature of the solvent for a period of 10 minutes to 15 hours. The preferred solvents for the condensation include dichloromethane or other chlorinated hydrocarbons, DMF, benzene-diethyl ether, diethyl ether-water and dioxan-water.

The compounds of formula IX may be prepared by reaction of an amino acid with a nitrogen heterocycle of formula VII



wherein



has its previous significance and where the amino acid and the compounds of formula VII are optionally protected. The reaction of the amino acid with the compound of formula VII is carried out for instance as are coupling reactions of amino acids in the preparation of peptides and according to methods of protection, activation, coupling and deprotection or partial deprotection described in the literature (Houben Weyl, Methoden Der Organischen Chemie Vol. 15 Parts 1 & 2).

For instance the aminoacyl amide compounds of formula IX starting materials required for the condensation reaction can be prepared by protecting the α -amino group of the amino acid via acetylation, formylation, phthaloylation, trifluoroacetylation,

p-methoxybenzyloxycarbonylation, benzoylation, benzyloxycarbonylation, t-butoxycarbonylation, arylsulfonylation, or tritylation and then condensing the formed N^α-substituted amino acid with a nitrogen heterocycle of formula VII to give a protected form of IX by a conventional process such as the acid chloride method, azide method, mixed anhydride method, activated ester method, or carbodiimide method, with or without additives such as hydroxysuccinide, hydroxybenztriazole, diethyl phosphite or the like, and thereafter selectively removing the protective groups to give a compound of formula IX.

Compounds of formula IX wherein



is a residue of formula IV or V and wherein X, Y, Q, Z, q, m, n, j and h have their previous significance are new compounds and form part of the invention. Preferred among such compounds are those in which amino acid residue Aa has the formula XVI or XVII.

In a second process, compounds of formula I may be prepared by reaction of arylsulfonyl amino acid compounds of formula VI, wherein Ar has its previous significance, with a nitrogen heterocycle of formula VII



(VII)

wherein



has its previous significance

and where the compounds of formulae VI and VII are optionally protected. Where the residue ArSO₂ in Compound I comprises a partially hydrogenated aromatic or heterocyclic system, the compound VI may contain hydrogenatable double bonds.

The reaction of a compound of formula VI with a heterocycle of formula VII is carried out for instance under reaction conditions known for coupling amino acids to form peptides and according to methods described in the literature (Houben Weyl, Methoden Der Organischen Chemie, Vol.15, Parts 1 and 2).

In the above formulae, protected species are typically protected on α-amino groups by

benzyloxycarbonyl or t-butoxycarbonyl.

For instance the compounds of formula I may be prepared by the condensation of an N^{α} -arylsulfonyl aminoacyl halide, preferably a chloride, a mixed anhydride, or a similar activated species derived in situ from N^{α} -arylsulfonyl amino acid VI with at least an equimolar amount of cyclic nitrogen base derivative (VII). The condensation reaction can be carried out with or without an added solvent in the presence of a base. Solvents such as dimethylformamide (DMF) or dimethylacetamide (DMAc) or halogenated solvents such as chloroform or dichloromethane may be used. The amount of the solvent to be used is not critical and may vary from about 5 to 100 times the weight of the N^{α} -arylsulfonyl amino acid (VI). In the other cases the activating principle such as diethyl phosphite may be the solvent.

When the activated species is an N^{α} -arylsulfonyl aminoacyl halide it may be prepared by reacting an N^{α} -arylsulfonyl amino acid VI with at least an equimolar amount of a halogenating agent such as thionyl chloride, phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride or phosphorus tribromide. The halogenation may be carried out with or without an added solvent. The preferred solvents are chlorinated hydrocarbons such as chloroform and dichloromethane, and ethers such as tetrahydrofuran and dioxan. Preferred reaction temperatures are in the range of -10°C to room temperature. The reaction time is not critical, but varies with the halogenating agent and reaction temperature. In general, a period of 15 minutes to 5 hours is operable.

Alternatively compounds of formula I may be prepared by reaction of N^{α} -arylsulfonyl amino acid of formula VI with nitrogen heterocycles of formula VII in the presence of a condensing agent such as a carbodiimide, for instance dicyclohexyl-carbodiimide in the presence or absence of an activating species such as hydroxybenzotriazole or diethyl phosphite and in the presence of a base. The base used in the above reactions may be either an organic base such as Huenig Base, triethylamine, N-methylmorpholine, or pyridine or an inorganic base such as sodium hydroxide or potassium carbonate. The condensation reaction may be carried out at a temperature between -10° and the boiling point of the solvent. Preferred condensation reaction temperatures are in the range from -10°C to room temperature. The reaction time is not critical, but varies with the derivative (VII) employed. In general, a period of from 5 minutes to 10 hours is operable.

When the product of formula I is obtained from the condensation reaction in protected form, for example a protected form of formula Ia



it may be purified by extraction and the solvent removed by such standard means as evaporation under reduced pressure and then converted to the compound of formula I by removing the protecting group by means of acidolysis or hydrogenolysis. The acidolysis is generally effected by contacting the protected form of I and an excess of an acid such as hydrogen fluoride, hydrogen chloride, hydrogen bromide or trifluoroacetic acid, without a solvent or in a solvent, such as an ether e.g. tetrahydrofuran or dioxan, an alcohol e.g. methanol or ethanol or acetic acid at a temperature of -10°C to 100°C , and preferably at room temperature for a period of 30 minutes to 24 hours. The products are isolated by evaporation of the solvent and the excess acid, or by trituration with a suitable solvent followed by filtration and drying. Because of the use of excess acid, the products are in certain cases the acid addition salts of the compounds of formula I, which can easily be converted to a free amide by neutralisation. When the protected compound of formula I contains the benzoxycarbonyl protection group the removal is readily accomplished by hydrogenolysis. At the same time any benzyl ester moiety is converted to the carboxyl group by the hydrogenolysis. Hydrogenation also serves to specifically convert certain aryl functions to the hydrogenated form in those compounds incorporating such an element of structure, for instance 3-methylquinolinyl (MQ) to 3-(RS)-methyl-1,2,3,4-tetrahydroquinolinyl.

The hydrogenolysis is effected in an inert reaction solvent, e.g. methanol, ethanol, tetrahydrofuran or dioxan optionally in the presence of an acid such as acetic acid and in the presence of a hydrogen-activating catalyst e.g. Raney nickel, palladium or platinum, in a hydrogen atmosphere at a temperature of 0°C to the boiling temperature of the solvent for a period of 2 hours to 120 hours. The hydrogen pressure is not critical, and atmospheric pressure is sufficient. The products of formula I are isolated by filtration of the catalyst followed by evaporation of the solvent. They may be purified by trituration or recrystallisation from a suitable solvent, such as ethyl acetate, diethyl ether-tetrahydrofuran, diethyl ether-methanol and water-methanol, or may be chromatographed on silica gel, ion-exclusion gels or reverse-phase liquid chromatography supports.

In those cases where the initial product of formula I contains a protected carboxylic acid or alcohol, it is well recognised in the art that the carboxylic acid or alcohol can be prepared from the ester derivative by conventional hydrolysis or acidolysis methods. The conditions under which esterification, hydrolysis or acidolysis can be carried out will be apparent to

those skilled in the art.

Methods C, D and E in the Synthetic Schemes above refer to those cases where a compound of formula I is made by Method A or B and it is then modified in one of the three parts of the molecule (A, B and C). These modifications may be to change one substituent for another, or to add a substituent, or to change a compound ABC which does not fit the definition of formula I above into a compound ABC which does fit that definition.

The modification processes are known per se and are described in the literature.

Examples of modifications falling under Method C are oxidation; alkylation; hydrolysis; carrying out a Wittig reaction on an aldehyde; converting an aldehyde to a hydroxyiminomethyl oxime; and converting an oxime to a tetrazolyl group via cyano.

Examples of modifications falling under Method D include converting a chloro to amino; and cyclising an aliphatic group to a heterocyclic ring.

Examples of modifications falling under Method E include esterification and amide coupling.

N^α-Arylsulfonyl aminoacyl amides (I) of this invention in certain cases form acid addition salts with any of a variety of inorganic and organic acids. Some of the N^α-arylsulfonyl aminoacyl amides containing a free carboxyl group form salts with any of a variety of inorganic and organic bases.

The product of the reactions described above can be isolated in the free form or in the form of salts. In addition, the product can be obtained as acid addition salts by reacting one of the free bases with an acid, such as hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, acetic, citric, maleic, succinic, lactic, tartaric, gluconic, benzoic, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic acid or the like. In a similar manner, the product can be obtained as salts by reacting the free carboxylic acid with a base, such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, triethylamine, procaine, dibenzylamine, N,N'-dibenzylethylenediamine, N-ethylpiperidine or the like.

Likewise, treatment of the salts with a base or acid results in a regeneration of the free amide.

Compounds of formula VI wherein Ar has its previous significance may be prepared by reacting an amino acid which may be optionally protected with an aryl sulfonic acid derivative of formula VIII as defined above in the presence of a base. The reaction is carried

out under conditions well known to those skilled in the art, generally in an inert solvent and in the presence of an excess of an organic or inorganic base as hereinbefore described and at a temperature of 0°C to the boiling point of the solvent.

Compounds of formula VIII where Ar is a residue of formula II or a residue of formula III wherein R¹, R², R³, R⁴, R⁵, R¹⁰, R¹¹, R¹² and R¹³ have their previous significance and W is a halogen may be prepared by methods described in the literature (Houben Weyl, Methoden Der Organischen Chemie Vol IX). For instance the sulfonyl halides may be prepared from the corresponding sulfonic acids of formula VIII where W is a hydroxyl group or a corresponding alkali or alkaline earth salt of formula VIIIa or a similar salt by treatment with a halogenating agent in the presence or absence of a solvent and optionally at elevated temperature, and with applied ultrasound.

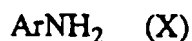
Examples of suitable halogenating agents include phosphorus halides such as phosphorus trichloride, phosphorus tribromide, phosphorus pentachloride, phosphorus pentabromide and phosphorus oxychloride; phosgene, benzotrichloride, thionyl chloride, chlorosulfonic acid, sulfur dichloride, sulfur and chlorine, chlorine and fluorosulfonic acid.

Suitable solvents for the reaction include dimethylformamide (DMF), dimethylacetamide (DMA), 1,3-dimethyl-2-imidazolidinone (DMID), and pyridine.

The reaction is conveniently carried out between -10°C and the boiling point of the solvent. It is advantageous to disperse or dissolve the sulfonic acid or its salt in the solvent whilst applying ultrasound.

After the reaction is complete, the reaction product is poured into ice water and then extracted with a solvent such as ether, benzene, ethyl acetate, chloroform or the like. Arylsulfonyl chlorides may also be prepared by chlorosulfonylation of aromatic hydrocarbons. The arylsulfonyl halide can be purified by recrystallisation from a suitable solvent such as hexane, benzene or the like.

In variations of this transformation the sulfonyl halide of formula VIII may be prepared in a single pot reaction from the corresponding arylamine of formula X



or aryl halide of formula XI



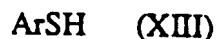
With ArNH_2 of formula X as the starting material, diazotisation followed by treatment with sulfur dioxide and chlorine in the presence of a catalyst, for example a copper halide such as cupric chloride and a quaternary ammonium halide such as tetrabutyl ammonium chloride, yields the desired sulfonyl chloride.

With ArHal^1 of formula XI as the starting material the halogen Hal^1 is replaced by lithium using an organo lithium reagent. Subsequent treatment with sulfur dioxide followed by halogenation for instance using an N-halo imide yields the desired arylsulfonyl halide VIII.

Alternatively, sulfonyl halides of formula VIII may be prepared from the corresponding parent aromatic compound of formula XII

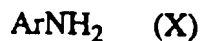


by halo sulfonation according to methods well known in the art using for instance chlorosulfonic acid, or sulfonyl chloride or from the corresponding thiols of formula XIII



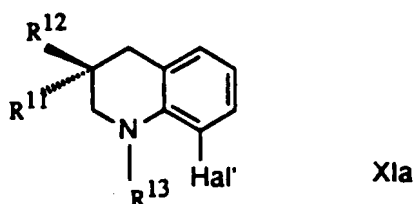
by oxyhalogenation.

Arylamines of formula X



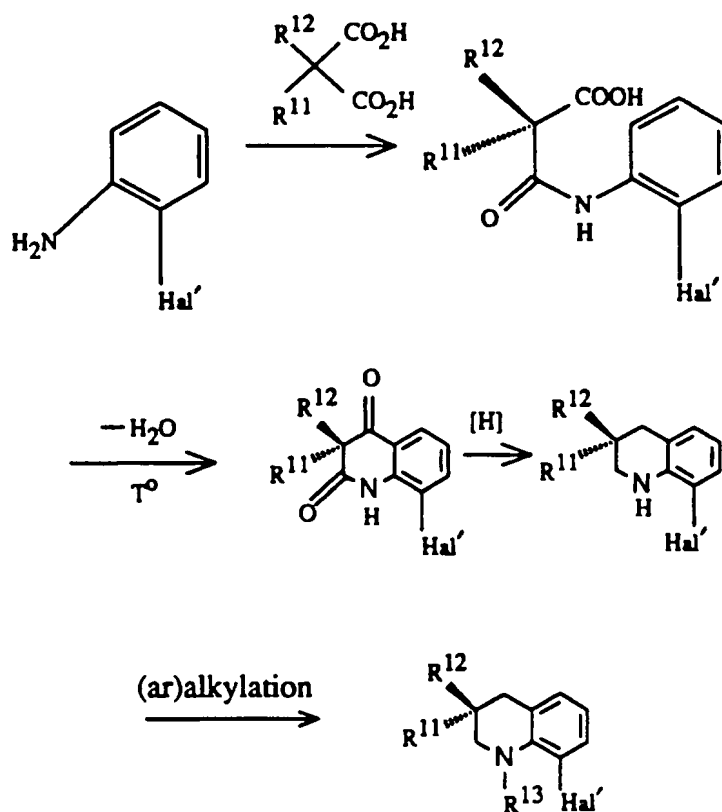
wherein Ar is a residue of formula II wherein $\text{R}^1 - \text{R}^5$ have their previous significance may be prepared by alkylation of aniline or substituted anilines using Friedel Crafts conditions as described for instance in European Patent 69065 (Ciba-Geigy).

Suitable derivatives ArHal^1 of formula XI for conversion to the corresponding sulfonyl chloride are those of formula XIa

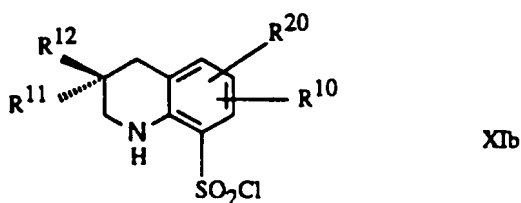


wherein R^{11} , R^{12} and R^{13} have their previous significance and Hal^1 is chlorine, bromine or iodine. Compounds of formula XIa may be prepared by the sequence of reactions shown in Scheme 1.

Scheme 1

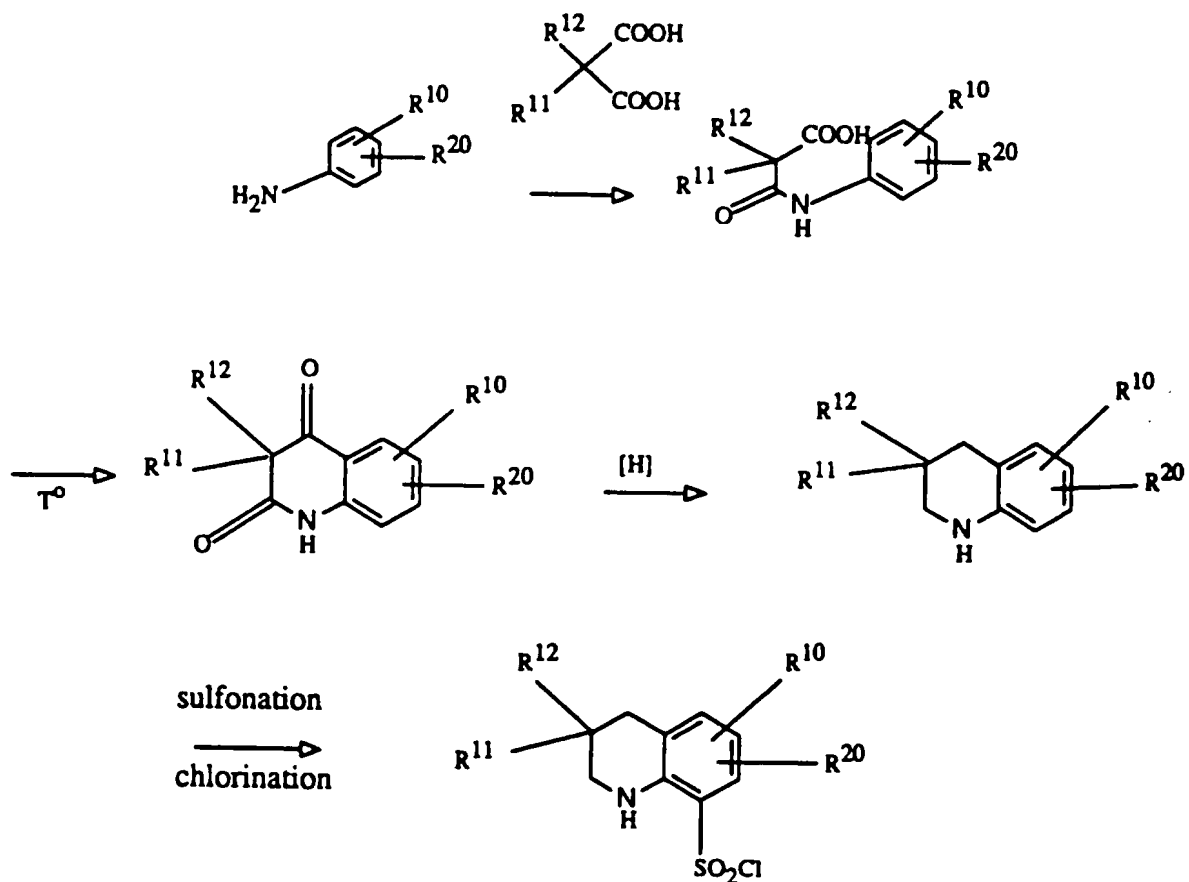


Compounds of formula XIb

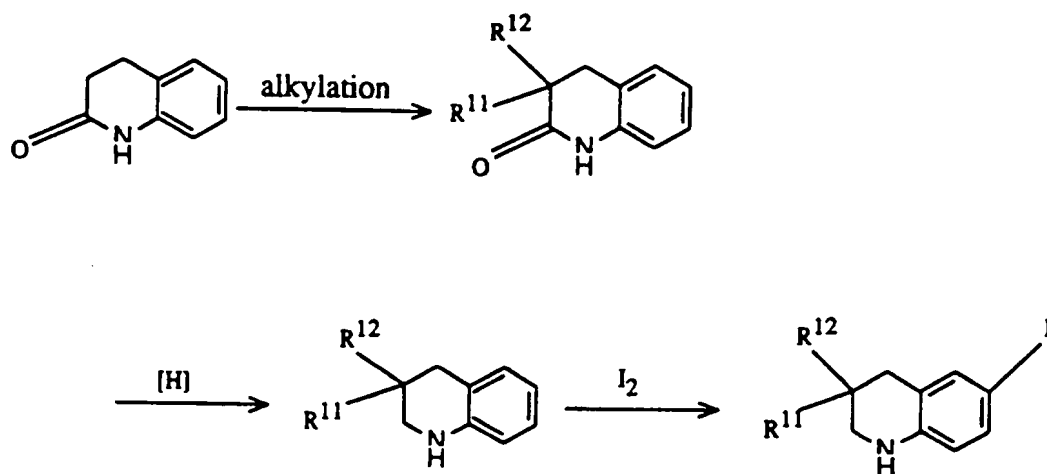


wherein R^{11} , R^{12} , R^{10} and R^{20} have their previous significance may be prepared by the sequence of reactions shown in Scheme 2.

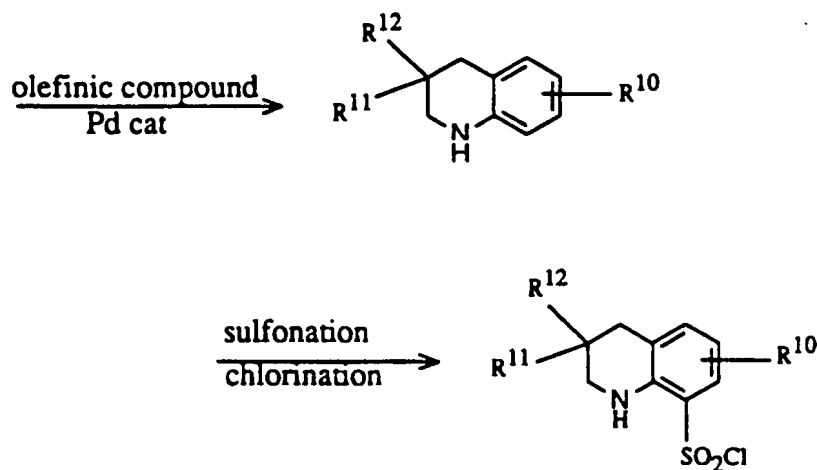
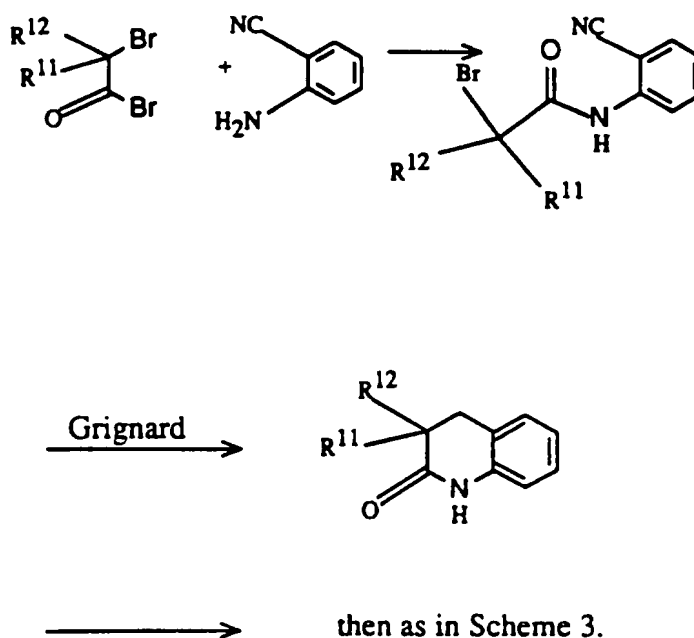
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Scheme 2

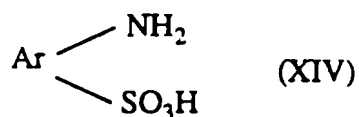
Sulfonyl halides of formula VIII may also be prepared by the following schemes 3 and 4.

Scheme 3

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Scheme 4

Compounds of formula VIII where Ar is a residue of formula II or a residue of formula III wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^{10} , R^{11} , R^{12} and R^{13} have their previous significance and W is a hydroxy group may be prepared by methods described in the literature (Houben Weyl, Methoden Der Organischen Chemie Vol. IX). For instance by sulfonation of an aromatic compound of formula XII, ArH or by deamination of an amino sulfonic acid of formula XIV

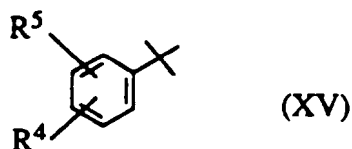


Suitable reagents for sulfonation include sulfuric acid, oleum, sulfur trioxide and complexes of sulfur trioxide, for instance the pyridine complex, acid sulfates such as potassium hydrogen sulfate, and chlorosulfonic acid. The sulfonation may be carried out with or without the presence of a catalyst. Catalysts may include metal salts, such as mercury salts or acids such as hydrogen fluoride or Lewis acids such as boron trifluoride. The reaction may be carried out in the presence or absence of a solvent inert under the reaction conditions and at a temperature between 0°C and the boiling point of the solvent.

When the sulfonic acid of formula VIII is produced by de-amination of an amino sulfonic acid of formula XIV the de-amination may be achieved by diazotisation followed by reduction with hypophosphorous acid. Salts of the sulfonic acids may be made by neutralisation of the free acid with the appropriate base.

Amino sulfonic acids of formula XIV where Ar has its previous significance may be prepared by aralkylation of amino sulfonic acids using Friedel Crafts conditions using the method described for instance in European Patent 69065, or by aralkylation of amino phenyl sulfonic acids in the absence of a catalyst and in solution in water or a mixture of water and a water-miscible solvent.

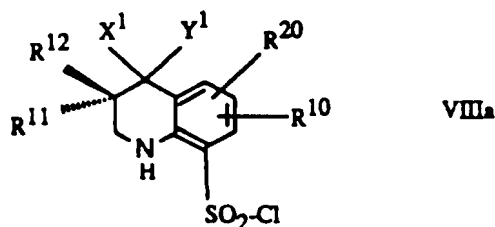
Depending on the route selected aromatic sulfonic acids of formula VIII where Ar is a residue of formula II the sulfonic acid residue in the ortho meta or para position relative to the residue XV



may be obtained and aromatic sulfonic acids of formula VIII where Ar is a residue of formula III with the sulfonic acid residue in the 8-position may be obtained.

Compounds of formula VI wherein Ar is an aryl residue of formula II or a quinolyl residue of formula III wherein R¹⁰, R²⁰, R¹¹, R¹² and R¹³ have their previous significance are new compounds and form part of the invention. Preferred among such compounds are those in which amino acid residue Aa has the formula XVI or XVII.

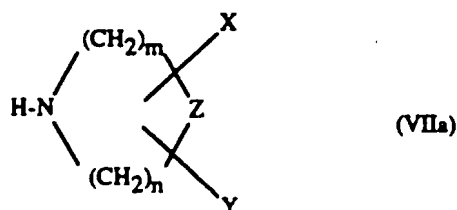
Compounds of formula VIIIa are new compounds and form part of the invention:



where $R^{11} = R^{12} =$ methyl or ethyl; $R^{11} =$ hydrogen and $R^{12} =$ methyl; $R^{11} =$ methyl and $R^{12} =$ hydrogen; or where one of R^{11} and R^{12} is hydrogen and the other is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or sec-butyl (other than the RS monomethyl compound) and X^1 and Y^1 are both H, one is H and one is OH or together are = O are new and form part of the invention. Preferably X^1 and Y^1 are both H.

Compounds of formula VII may be prepared by methods well known to those skilled in the art, for instance substituted piperidines may be obtained by reduction of the corresponding substituted pyridines. The starting substituted pyridines are either known or may be prepared by known methods. For instance carboxy substituted pyridines may be reduced to give hydroxy alkyl piperidines.

Compounds of formula VII which have the formula VIIa are new compounds



in which X is hydrogen or C_1 - C_5 alkyl;

Y is $(C_q H_{2q})-Q$ or $(C_w H_{2w+1-y-z})F_y OH_z$ where Q is COR^{14} , CO_2R^{14} , $CONR^{15}R^{16} SO_3H$, OR^{14} , $OCOR^{14}$, $PO(OR^{14})_2$, $NR^{15}R^{16}$, SR^{14} or halogen wherein R^{14} , R^{15} and R^{16} are independently hydrogen C_1 - C_5 alkyl, C_5 - C_8 cycloalkyl or C_7 - C_{11} aralkyl groups, or R^{15} and R^{16} together with the nitrogen atom to which they are bound form a 5 or 6 membered azacycloalkyl or oxazacycloalkyl, q is 0 or an integer from 1 to 8, w is an integer from 1 to 8, y is an integer from 1 to 17 and z is 0 or 1 and the residue $C_q H_{2q}$ may be optionally substituted by OH or interrupted by oxygen, sulfur, oxycarbonyl O.CO, carbonyloxy CO.O, aminocarbonyl NHCO, sulfonamido, $NHSO_2$ or carboxamido CONH, Z is a direct

bond, oxygen or nitrogen optionally substituted by X or Y, m is an integer from 2 to 4, n is an integer from 2 to 4 and m + n is 4 to 6 providing that when Q is a group COR^{14} , CO_2R^{14} , $\text{CONR}^{15}\text{R}^{16}$, SO_3H , OR^{14} , $\text{NR}^{15}\text{R}^{16}$ or SR^{14} , or when Q is a group O.COR^{14} and Z is nitrogen, and q is not 1 and if q is 2 to 4 then the residue C_qH_{2q} is interrupted by oxygen sulfur, oxycarbonyl O.CO , carboxyloxy CO.O , aminocarbonyl NHCO , or carbamoyl CONH .

Compounds of formula VIIa may be prepared by reduction of corresponding aromatic compounds or by ring closure methods described in the references below. For instance functionally substituted piperidines and piperazines of formula I carrying a group $(\text{C}_q\text{H}_{2q})\text{-Q}$ may be prepared by reduction of the corresponding pyridines and pyrazines. Such procedures are described in chemistry of Heterocyclic Compound Ed: A. Weissberger - Pyridine and its derivatives; Comprehensive Heterocyclic Chemistry, Katritzky and Rees Vol 2; and Heterocyclic Compounds Vol 6 Elderfield.

A functional group Q may be converted into a different functional group Q by standard interconversion methods. For instance where the functional group Q is a carboxylic acid it may be converted to an ester or an amide by treatment with an alcohol or an amine. Conversely where the functional group is a carboxylic ester or carboxylic amide it may be hydrolysed to the acid using for instance acid or basic conditions.

Where the functional group Q is an alcohol or an amine it may be acylated using a (functional) carboxylic acid and a condensing agent or by use of an activated species such as an acid halide or anhydride.

The reaction may be carried out in a solvent and in the presence or absence of a catalyst. Examples of catalyst are acids such as hydrogen chloride, or toluenesulfonic acid.

If desired the nitrogen(s) of the ring may be protected whilst a side chain functional group is reacted. Examples of protecting groups for the nitrogens are t-butoxycarbonyl and benzyloxycarbonyl.

Compounds of formula 1 wherein Q is a COOH group may also be prepared from a corresponding alcohol by oxidation of a CH_2OH group to a COOH group, for instance by using an oxidising agent such as pyridinium dichromate or the like.

Compounds in which the residue C_qH_{2q} is interrupted by an oxygen or sulfur atom may be made for instance by reaction of a piperidine or piperazine alkyl halide with a functional

alcohol or thiol in the presence of a catalyst such as sodium.

The compounds of formula I provide interesting compounds which contain potent and orally bioavailable inhibitors of serine proteases, especially thrombin and trypsin.

The compounds of the present invention are useful in compositions, combinations and methods for the treatment and prophylaxis of various diseases attributed to thrombin-mediated and thrombin-associated functions and processes. These include myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, disseminated intravascular coagulation, peripheral arterial occlusion, restenosis following arterial injury or invasive cardiological procedures including percutaneous transluminal coronary angioplasty, atrial fibrillation, acute or chronic atherosclerosis, edema and inflammation, various cell regulatory processes (e.g. secretion, shape changes, proliferation), cancer and metastasis, and neurodegenerative diseases.

The thrombin inhibitors of the present invention may be formulated into pharmaceutically useful compositions, such as by mixing with a pharmaceutically acceptable carrier or diluent. These compositions may be used for treating or preventing thrombotic diseases in a patient.

According to an alternate embodiment of the present invention, the thrombin inhibitors may be employed in compositions for treating thrombotic disease, and for decreasing the dosage of a thrombolytic agent required to establish reperfusion or prevent reocclusion in a patient. Additionally, the thrombin inhibitors of this invention may be used in compositions for decreasing reperfusion time or the incidence of acute reocclusion in a patient treated with a thrombolytic agent. These compositions may comprise a pharmaceutically effective amount of a thrombin inhibitor of the present invention and a pharmaceutically effective amount of a thrombolytic agent.

In these compositions, the thrombin inhibitor and the thrombolytic agent work in a complementary fashion to dissolve blood clots, resulting in decreased reperfusion times and incidence of acute reocclusion in patients treated with them. The thrombolytic agent dissolves the clot, while the thrombin inhibitor prevents newly exposed, clot-entrapped or clot-bound thrombin from regenerating the clot. The use of the thrombin inhibitor in the compositions of this invention advantageously allows the administration of a thrombolytic reagent in dosages previously considered too low to result in thrombolytic effects if given alone. This avoids some of the undesirable side effects associated with the use of thrombolytic agents, such as bleeding complications.

Thrombolytic agents which may be employed in the combinations and compositions of the present invention are those known in the art. Such agents include tissue plasminogen activator purified from natural sources, recombinant tissue plasminogen activator, streptokinase, urokinase, prourokinase, anisolated streptokinase plasminogen activator complex (ASPAC), animal salivary gland plasminogen activators, hybrids of the above and known, biologically active derivatives. The thrombin inhibitor and the thrombolytic agent may be in the same or in separate dosage forms which are administered separately, but concurrently or sequentially. In sequential administration, the thrombin inhibitor may be given to the patient at a time from 5 hours before to 5 hours after administration of the thrombolytic agent. Preferably, the thrombin inhibitor is administered to the patient at a time from 2 hours before to 2 hours after administration of the thrombolytic agent.

The compounds of the invention may also be used in combinations and compositions with other antithrombotic drugs such as aspirin, fibrinogen receptor blockers, platelet aggregation inhibitors and the like.

The compositions of the invention may be administered to a patient in various ways e.g. enterally such as orally or rectally, parenterally or topically. The compositions will be formulated using adjuvants and diluents suitable for the desired method of administration. Thus the compositions may be administered intravenously or intra-arterially as bolus or by continued infusion, intramuscularly - including paravertebrally and periarticularly - subcutaneously, intracutaneously, intra-articularly, intrasynovially, intrathecally, intra-lesionally, periostally or by oral, nasal, or topical routes. In addition they may be given directly into the central nervous system. Moreover they may be applied transdermally by either passive or active methods, including by iontophoresis.

Parenteral compositions are preferably administered intravenously either in a bolus form or as an infusion. For parenteral administration, the thrombin inhibitor may be either suspended or dissolved in a sterile vehicle, optionally together with other components, and sterilized before filling into a suitable vial or ampule and sealing. Preferably, adjuvants such as a local anesthetic, preservatives, stabilizers, solution promoters and/or buffers may also be dissolved in the vehicle. The composition may then be frozen and lyophilized to enhance stability. In the case of suspensions, a surfactant or wetting agent and/or other adjuvant as mentioned above may be included in the composition to facilitate uniform distribution of its components.

Tablets and capsules e.g. gelatin capsules for oral administration may comprise the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol

cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salts and/or polyethylene glycol; for tablets also c) binders, e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired, d) disintegrants, e.g. starches, starch derivatives such as sodium starch glycolate, croscarmellose, agar, alginic acid or its sodium salt, or effervescent mixtures; e) wetting agents such as sodium lauryl sulphate; and/or f) absorbents, colourants, flavours and sweeteners. Suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents.

Oral liquid preparations may be in the form of aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstruction with water or another suitable vehicle before use. Such liquid preparations may contain conventional additives. These include suspending agents; such as sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel or hydrogenated edible fats; emulsifying agents, such as lecithin, sorbitan monooleate, polyethylene glycols, or acacia; non-aqueous vehicles, such as almond oil, fractionated coconut oil, and oily esters; and preservatives, such as methyl or propyl p-hydroxybenzoate or sorbic acid.

Compositions formulated for topical administration may, for example, be in aqueous jelly, oily suspension or emulsified ointment form.

Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.

Transdermal systems may be made by applying an adhesive layer to a base layer, e.g. a peel-off protective layer, applying a reservoir to the base layer, the reservoir containing the active ingredient and optionally a polymeric material for forming a porous or permeable membrane and/or a penetration enhancer, and then applying an impermeable outer layer on top.

The dosage of active compound administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration.

A preferred pharmaceutically effective dose of the thrombin inhibitor of this invention is

from 0.01mg/kg body weight of the patient to be treated to 50mg/kg body weight, preferably from 0.1 to 1.0mg/kg.

The amount used depend on the method of administration. Normally lower amounts are needed for parenteral administration than for enteral administration. The dose for infusions however may be higher than the range given, preferably from 0.01 to 1.0mg/kg/hr. When a thrombolytic agent is also used a pharmaceutically effective dose of the thrombolytic agent may be between 10% and 80% of the conventional dosage range, i.e. the dosage used when that agent is employed in a monotherapy.

The compounds of the invention may also be used in the form of conjugates with materials such as polyethylene glycol. This would modify the pharmacokinetic properties of the compounds and result in lower doses being needed, or less frequent doses.

The thrombin inhibitors of the invention may also be used in compositions and methods for coating the surfaces of invasive or extra-corporeal devices, resulting in a lower risk of clot formation or platelet activation in patients receiving or using such devices. Surfaces that may be coated with the compositions of this invention include, for example, prostheses, artificial valves, vascular grafts, stents tubing, membranes and catheters. Methods for coating these devices are known to those of skill in the art. These include chemical cross-linking or physical adsorption of the thrombin inhibitor-containing compositions on to the surfaces of the devices.

Compositions containing the thrombin inhibitors of this invention may also be used in the treatment of tumor metastases, as indicated by the inhibition of metastatic growth.

Examples of metastatic tumors which may be treated by the thrombin inhibitors of this invention include carcinoma of the brain, carcinoma of the liver, carcinoma of the lung, osteocarcinoma and neoplastic plasma cell carcinoma.

Compositions containing the thrombin inhibitors of the invention may also be used to inhibit thrombin-induced endothelial cell activation, including the repression of synthesis of mediators, including platelet-activating factor (PAF), eicosanoids, endothelial-derived relaxing factor (EDRF) and endothelin, by endothelial cells. The compositions have important applications in the treatment of diseases characterized by thrombin-induced inflammation and edema, which is thought to be mediated by PAF. Such diseases include adult respiratory distress syndrome, septic shock, septicemia, reperfusion damage, and for treating or preventing septicemia and other diseases.

The thrombin inhibitors of the invention or compositions comprising them, may also be used as anticoagulants for extracorporeal blood, for instance in such processes as dialysis procedures, blood filtration, or blood bypass during surgery at doses from 0.01 to 1.0mg/kg as well as in blood products which are stored extracorporeally for eventual administration to a patient and blood collected from a patient to be used for various assays. Such products include whole blood, plasma, or any blood fraction in which inhibition of coagulation is desired.

The amount or concentration of thrombin inhibitor in these types of compositions is based on the volume of blood to be treated or, more preferably, its thrombin content, and may be from 0.01mg/60ml of extracorporeal blood to 5mg/60ml of extracorporeal blood.

The thrombin inhibitors of this invention may also be used to inhibit clot-bound thrombin, which is believed to contribute to thrombus growth and clot accretion, and to prevent thrombus extension. This is particularly important because commonly used anti-thrombin agents, such as heparin and low molecular weight heparin, are ineffective against clot-bound thrombin.

Finally, the inhibitors of this invention may be used for treating neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, inflammatory diseases and cerebral ischaemia.

The invention is illustrated by the following Examples, in which the abbreviations used have the following meanings.

Abbreviations

BTMA. ICl_2	Benzyltrimethylammonium iodine dichloride
DAST	Diethylamino sulfur trifluoride
DCC	Dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMID	1,3-Dimethyl-2-imidazolidinone
HOBt. H_2O	Benzotriazol-1-ol hydrate
Huenig Base	Ethyl-diisopropylamine
Ishikawa reagent	Diethyl-(1,1,2,3,3,3-hexafluoro-propyl)-amine
Lawesson's reagent	p-Methoxyphenylthionophosphine sulphide dimer
LDA	Lithium diisopropylamide
NaHMDS	1,1,1,3,3,3-Hexamethyldisilazane sodium salt
NMM	N-Methyl morpholine
PyBOP	Benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofuran

INTERMEDIATE 1-1

a) To an ethereal diazomethane solution at 0°C is added a finely powdered suspension of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (448mg) in methanol/ethanol (15ml, 1:1 by vol.) over 15-20 minutes. The mixture is allowed to warm to 10°C over 2 hours, with occasional agitation. Excess of diazomethane is destroyed by addition of acetic acid. Ether (20ml) is added and the solution is washed with water (25ml). The aqueous phase is extracted with ether (10ml) and the combined organic extracts washed with brine (10ml) and dried (MgSO_4). Evaporation of the solvent gives a pale yellow oil (374mg). This is purified on a column of silicagel which is eluted with ether:hexane (1:3 by volume). Combination of appropriate fractions yields, after evaporation, 1,3(RS)-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid methyl ester as a colourless oil.

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b) 1,3(RS)-Dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid methyl ester (107mg) is dissolved in ethanol:water (5:1 by vol., 6ml), aqueous sodium hydroxide (M, 0.45ml) is added and the mixture is stirred at 20°C for 24 hours. The mixture is evaporated to give a pale yellow oil which is dissolved in water (10ml), extracted with ether (2x10ml), acidified with aqueous hydrochloric acid (M, 3ml) and extracted with dichloromethane (15x10ml). The combined extracts are dried (MgSO₄) and evaporated to give 1,3(RS)-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid as a white solid.

c) 1,3(RS)-Dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (80mg) is suspended in acetonitrile (2ml) at 20°C and pyridine (25μl) and then phosphoryl chloride (28μl) are added. The mixture is stirred 20°C for 2 hours. Additional phosphoryl chloride (28μl) is added after 2 hours. After a further 2.5 hours the mixture is heated to 90-95°C for 2 hours when more phosphoryl chloride (56μl) is added and the mixture heated at reflux for a further 2 hours, cooled and evaporated to give a yellow semi-solid oil which is dissolved in ethyl acetate (20ml) and washed with water (2x5ml), saturated aqueous sodium bicarbonate (2x5ml), dried (MgSO₄) and evaporated to give 1,3(RS)-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride.

INTERMEDIATE 1-2

a) Dimethylmalonic acid (259g) is dissolved in THF (500ml), thionyl chloride (172ml) is added and the mixture is heated at reflux for 2 hours and then cooled in ice. To this solution is added with stirring during 75 min at <10°C a solution of 4-chloroaniline (500g) in ether (500ml). The mixture is stirred for 30 minutes and ether (500ml) is added. The mixture is washed with aqueous hydrochloric acid (M, 3x1l) and extracted with aqueous sodium hydroxide (M, 3x1l). The combined basic extracts are acidified with conc. aqueous hydrochloric acid. An oil separates which, on keeping the mixture overnight at room temperature, partially crystallises. The crystals are collected by filtration and washed with water. Addition of more water to the stirred filtrate results in solution of the oil and the production of more crystals of N-(4-chloro-phenyl)-2,2-dimethyl-malonamic acid, m.p. 169-170°C.

- b) N-(4-Chloro-phenyl)-2,2-dimethyl-malonamic acid (150g) is added in one charge to a stirred solution of phosphorus pentoxide (50g) in methane sulphonic acid (1l) at 70°C under nitrogen. The mixture is stirred at 70°C for 16 hours, cooled to room temperature and poured into ice-water (7.5l) and the resulting suspension stirred for 1 hour to afford material which is recovered by filtration and washing with cold water. It is resuspended in cold water (4l) and stirred for 45 minutes, collected by filtration, washed and dried in vacuo at 50°C (P_2O_5) to yield 6-chloro-3,3-dimethyl-1.H.-quinoline-2,4-dione, m.p. 227-8°C.
- c) Aluminium trichloride (86g) is dissolved in dry ether (324ml) and lithium aluminium hydride (M in THF, 800ml) is added cautiously under vigorous stirring at room temperature. After stirring for a further 20 minutes, 6-chloro-3,3-dimethyl-1 H-quinolin-2,4-dione (71.5g) in dry THF (690ml) is added at a rate to maintain a gentle reflux. After stirring for a further hour at room temperature, the mixture is cooled to -10°C, water (2l) and then aqueous sodium hydroxide (M, 1l) are added cautiously to decompose the reagents and the ethereal layer collected by decantation. The residue and aqueous supernatant are gently stirred with portions of ether (500ml) which are collected by decantation until the extracts are colourless. The combined extracts are dried ($MgSO_4$), evaporated to dryness and dried in vacuo (NaOH pellets) to give a solid which is crystallised from aqueous methanol to yield 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline in two crops, m.p. 64-5°C.
- d) Pyridine/sulfur trioxide complex (161g) is added to a solution of 6-chloro-3,3-dimethyl-1,2,3,4- tetrahydro-quinoline (45.7g) in pyridine (1.72l) and the mixture is heated at reflux for 23 hours. After cooling, the reaction mixture is poured into water (2l) and the mixture extracted with ether (3x1l). The combined ethereal extracts are back-extracted with water (3x500ml) and the combined aqueous fractions are evaporated to dryness. Addition of aqueous hydrochloric acid (M, 4.16l) to the brown oil gives a buff solid. After stirring for a further 15 min, the solid is collected by filtration, washed cautiously with a small amount of ice-water and dried in vacuo (P_2O_5) to give 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid, m.p. 244-5°C.

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e) 6-Chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (2.0g) is suspended in acetonitrile (24ml) and ultrasonicated for 10 minutes. Pyridine (1.2ml) is added and the solution is covered with a blanket of nitrogen. After 10 minutes, phosphoryl chloride (1.34ml) is added dropwise and the mixture is stirred for 16 hours at 20°C. The solvents are evaporated and the residue partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase is washed with portions (25ml) of aqueous sodium bicarbonate and water (x2), dried (MgSO₄) and evaporated to give 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride which is dried in vacuo (NaOH pellets).

INTERMEDIATE 1-3

Method 1

a) 3,3-Dimethyl-3,4-dihydro-1H-quinolin-2-one (10g) and bromine (2.94ml) are dissolved in chloroform (150ml) and heated gently at reflux for 3 hours. The solvent is removed by evaporation and the recovered solid recrystallised from ethyl acetate/hexane to give 6-bromo-3,3-dimethyl-3,4-dihydro-1H-quinolin-2-one, m.p. 175-6°C.

b) Aluminium trichloride (6.52g) is dissolved in dry ether (50ml) under nitrogen, cooled to -20°C and lithium aluminium hydride (M in THF, 49ml) is added dropwise. The mixture is allowed to warm to 20°C and stirred for 30 minutes. 6-Bromo-3,3-dimethyl-3,4-dihydro-1H-quinolin-2-one (12.42g) dissolved in dry THF (100ml) under nitrogen is added dropwise to the LiAlH₄/AlCl₃ at -20°C (CaCl₂ tube). The stirred mixture is allowed to warm to 20°C and stirred for a further 20 hours. The mixture is cooled to -78°C and water (25ml) is added slowly. After stirring for 30 minutes, aqueous sodium hydroxide (M, 25ml) and water (100ml) are added and the mixture is extracted with ether (3x50ml). The combined extracts are washed with brine and water and dried (MgSO₄). Removal of the solvent gives 6-bromo-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline which is sufficiently pure (m.p. 74-5°C) for the next step.

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c) Dimethylformamide/sulfur trioxide complex (36g) is placed in a dry flask and immediately covered with nitrogen. 6-Bromo-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline (5.6g) dissolved in dry DMF (50ml), under nitrogen, is added to the DMF/sulfur trioxide complex via a septum. The reaction mixture is heated at 60°C under nitrogen for 2.5 hours, the DMF removed by distillation and the resultant solid washed with cold ethyl acetate. The dried product, 6-bromo-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (m.p. 198-9°C (decomp.)) is sufficiently pure for the next step.

d) 6-Bromo-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (4.19g), 10% palladium on charcoal (1g) and sodium bicarbonate (8.3g) are stirred in water (250ml) in an atmosphere of hydrogen (1 bar) for 2 hours at 20°C. The catalyst is removed by filtration and the filtrate evaporated to yield a solid residue which is dissolved in ethyl acetate/ethanol (2:1 by volume, 50ml) and the solution passed through a pad of silicagel to remove inorganic material. Evaporation of the eluate affords 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (m.p. >300 °C).

e) 3,3-Dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (750mg) is ultrasonicated for 15 minutes in DMID (4.6ml) under an atmosphere of nitrogen. Pyridine (0.7ml) is added over 20 minutes followed by phosphoryl chloride (1.1 ml) over 20 minutes. The reaction mixture is stirred at 20°C for 16 hours and then partitioned between ethyl acetate and water (100ml, 1:1 by volume). The phases are separated and the organic phase washed with a further portion (50ml) of water which is back-extracted with ethyl acetate (50ml). The combined organic phases are washed with saturated aqueous sodium bicarbonate (2x25ml), dried (MgSO₄) and the solvent removed by evaporation to yield 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride, unstable to prolonged storage, which is suitable for immediate use.

Method 2

a) 6-Chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (20g) is dissolved in a mixture of methanol (200ml) and triethylamine (50.4ml) and hydrogenated in the presence of 10% palladium on charcoal (4.0g) for 72 hours at 20°C. The catalyst is removed by filtration and the solvent removed by rotary evaporation to give crude 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulphonic acid as brown crystals which are stored in vacuo.

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b) Triphenylphosphine (38g) is dissolved in dichloromethane (200ml) and cooled to 0°C and a solution of sulfuryl chloride (15ml) in dichloromethane (15ml) is added during 15 minutes keeping the temperature of the stirred mixture below 5°C. The mixture is allowed to warm to room temperature and a solution of crude 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (34g) in dichloromethane (250ml) is added during 30 minutes with stirring. The mixture is stirred for 2 hours at 20°C and then extracted with water (500ml). The water extract is back-washed with dichloromethane (200ml), the combined organic layers are dried (MgSO_4) and the solvent removed by rotary evaporation. The residue is stirred with dry ether (400ml) for 1 hour at 20°C and the solid triphenylphosphine oxide removed by filtration and washed with ether (3x30ml). The combined ether solutions are dried by rotary evaporation and the residue stirred with dry ether (60ml) as above to remove more triphenylphosphine oxide. Evaporation of the resultant ether solution gives 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride as a yellow oil which is suitable for immediate use.

INTERMEDIATE 1-4

a) A solution of dimethylmalonic acid (9.8g) in dry THF (25ml) is treated with thionyl chloride (6.8ml) and heated at reflux for 2 hours. The reaction mixture is cooled to room temperature and added to a cooled (0-5°C) solution of 2-bromoaniline (26.0g) in dry ether (20ml) dropwise during 20 minutes. The mixture is stirred at room temperature for 30 minutes and then poured into ether (60ml). The solution is washed with aqueous hydrochloric acid (M, 2x 30ml) and extracted with aqueous sodium hydroxide (4M, 40ml). The combined aqueous extracts are acidified with aqueous hydrochloric acid (5M) and the resultant orange oil extracted with ether (2x40ml). The combined extracts are dried (MgSO_4) and the solvent evaporated to give N-(4-bromo-phenyl)-2,2-dimethyl-malonamic acid as a pale orange solid.

b) A solution of N-(4-bromo-phenyl)-2,2-dimethyl-malonamic acid (15.5g) in xylene (250ml) is treated with phosphorous pentoxide (15g) and heated at reflux for 7.5 hours. The mixture is cooled and the solvent decanted. The decantate is evaporated to give a yellow oil which is treated with ether (100ml). The resultant cream precipitate is collected by filtration. The filtrate is reduced in volume by evaporation and the ether precipitation is repeated twice.

The combined precipitates are recrystallised from ether-hexane to give 8-bromo-3,3-dimethyl-1.H.-quinoline-2,4-dione. The filtrate is reduced in volume and the recovered crude material purified by chromatography on a 29 column of silicagel eluting with ethyl acetate:hexane (1:9 by volume) to give a second crop of the dione.

c) Lithium aluminium hydride (M in THF, 2.0ml) is treated with a cooled (0-5°C) solution of aluminium chloride (2.7g) in dry THF (20ml). The mixture is stirred at 20°C for 5 minutes. The mixture is treated with a solution of 8-bromo-3,3-dimethyl-1H-quinoline-2,4-dione (2.7g) in dry ether (40ml) dropwise at such a rate as to maintain a gentle reflux. The mixture is stirred at 20°C for 30 minutes. The mixture is poured into ether (30ml) and water (20ml) and aqueous sodium hydroxide (M, 20ml) are added. The separated aqueous layer is extracted with ether (40ml) and the combined extracts are washed with brine (30ml), dried (MgSO₄) and evaporated to give an orange oil which is purified on a column of silicagel eluting with ethyl acetate:hexane (1:9, by vol.) to give 8-bromo-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline as a clear oil which, on storage, gives a white solid.

d) A cooled (-78°C) solution of 8-bromo-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline (956mg) in dry ether (20ml) is treated with n-butyl lithium (2.5M in hexanes, 1.8ml) and stirred at -78°C for 35 minutes. Methyl iodide (1.0ml) is added and the solution is warmed slowly to room temperature and stirred for 3 hours. The mixture is quenched with water (40ml) and extracted with ether (2x30ml), the combined extracts washed with brine (20ml) and dried (MgSO₄). The ether and any residual methyl iodide are removed by evaporation. The residual oil is purified by chromatography on a column of silicagel which is eluted with ethyl acetate:hexane (15:985, by vol.) to give 8-bromo-1,3,3-trimethyl-1,2,3,4-tetrahydro-quinoline as a colourless oil.

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e) A cooled (-78°C) solution of 8-bromo-1,3,3-trimethyl-1,2,3,4-tetrahydro-quinoline (253 mg) in dry ether (10ml) is treated with n-butyl lithium (2.5M in hexanes, 0.44ml) and stirred at -78°C for 35 minutes. This solution is transferred, by syringe, into a cooled (-60°C), vigorously-stirred solution of liquid sulphur dioxide (5ml) in dry ether (10ml) dropwise during 5 minutes. The mixture is allowed to warm to room temperature (1 hour) and evaporated to dryness. The resultant yellow solid is suspended in dichloromethane (20ml) which is cooled to 0-5°C. N-Chlorosuccinimide (134 mg) is added and the resultant green suspension is allowed to warm to room temperature and stirred for 1.5 hours. The mixture is washed with water (20ml) and the aqueous washings are extracted with dichloromethane (10ml). The combined organic extracts are washed with brine (20ml) and dried (MgSO₄). Evaporation of the solvent gives an oil which is purified by chromatography on a column of silicagel eluted with ethyl acetate:hexane (1:19, by vol.) to give 1,3,3-trimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride as a yellow oil.

INTERMEDIATE 1-5

a) A suspension of sodium hydride (2.01g) in toluene (50ml) is treated at 20°C with a solution of 2(S)-bornane-10,2-sultam (9.85g) in a mixture of THF (25ml) and toluene (50ml) added over 30 minutes. The mixture is stirred for 1 hour. A thick mass forms. Propionyl chloride (4.4ml) in THF (20ml) is added over 20 minutes and the mixture stirred for 16 hours. Saturated aqueous ammonium chloride (50ml) is added and the mixture is poured into ether (50ml) and the separated aqueous layer washed with ether (2x25ml). The combined organic extracts are washed with portions (25ml) of water, brine and dried (MgSO₄). Evaporation of the solvent gives a white solid (14.9g) which is re-crystallised from methanol to afford N-propionyl-2(S)-bornane-2,10-sultam m.p. 149.0-150.7°C.

b) A cooled solution of N-propionyl-2(S)-bornane-2,10-sultam (10.26g) in THF (120ml) at -78°C (all under nitrogen) is treated with NaHMDS (M solution) over 5 minutes dropwise. The mixture is stirred for 1 hour at -78°C. 2-Nitrobenzylbromide (12.5g) in DMID (13.6ml) is added dropwise over 7-8 minutes, and the mixture is allowed to warm to 5°C over 3.5 hours and then stirred at 20°C for 16 hours. Water (40ml) is added and the mixture poured into ether (50ml) and water (25ml).

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The aqueous phase is extracted with ether (25ml) and the combined organic extracts are washed with portions (2x25ml) of water, brine and dried (MgSO_4). Evaporation of the solvent gives a viscous orange oil. This is purified by chromatography on a column of silicagel (ether:hexane = 1:1, by vol., then ether) to afford a pale yellow solid which is crystallised from methanol to give N-(2(R)-methyl-3-[2-nitrophenyl]-propionyl)-2(S)-bornane-2,10-sultam as pale yellow crystals, m.p. 126.5-127.5°C.

c) N-(2(R)-Methyl-3-[2-nitrophenyl]-propionyl)-2(S)-bornane-2,10-sultam (7.9g) is dissolved in THF:water (4:1, by vol., 150ml) at ice temperature (0-5°C) and treated with hydrogen peroxide (30% w/v, 18.5ml) followed by lithium hydroxide hydrate (3.64g). The mixture is stirred at 0-5°C for 1.3 hours and then at 20°C for 3.5 hours. Aqueous hydrochloric acid (M, 150ml) is added and the mixture is poured into dichloromethane (100ml). The aqueous phase is extracted with dichloromethane (2x50ml). The combined organic phases are extracted into 10% aqueous sodium bicarbonate (2x25ml). The combined aqueous extracts are acidified to pH 1-2 with aqueous hydrochloric acid (M) and extracted with ether (4x25ml), the combined extracts are dried (MgSO_4) and the solvent evaporated to give 2(R)-methyl-3-(2-nitrophenyl)-propionic acid as a pale yellow oil which is used directly in the next step.

d) A solution of 2(R)-methyl-3-(2-nitrophenyl)-propionic acid (3.9g) in ethanol (100ml) is treated with cyclohexene (9.75g) and 10% palladium on charcoal (3.8g) and heated at reflux for 55 minutes. The mixture is cooled to 20°C, filtered through a Celite pad to remove the catalyst and the filtrate evaporated to obtain a solid which is purified by chromatography on a column of silicagel (using ethanol:dichloromethane, 1:19, by vol.) to give 3(R)-methyl-3,4-dihydro-1H-quinolin-2-one as an off-white solid which is sufficiently pure for use in the next step. Recrystallisation from ether gives colourless crystals, m.p. 129.9 - 131.8°C.

e) 3(R)-Methyl-3,4-dihydro-1H-quinolin-2-one (1.98g) is dissolved in chloroform (33ml) and bromine (0.5ml) is added. The mixture is heated at reflux for 1 hour. After cooling to 20°C, evaporation of the solvent gives a yellow oil which is purified by chromatography on a column of silicagel using ether:hexane (65:35, by vol.) to afford 6-bromo-3(R)-methyl-3,4-dihydro-1H-quinolin-2-one, m.p. 147.0-148.3°C.

f) Aluminium chloride (1.198g) is added over 5-10 minutes to dry ether (10ml) at -10°C under nitrogen. Lithium aluminium hydride (M in THF, 8.35ml) is added to this solution and the resultant mixture stirred for 10 minutes at 20°C. 6-Bromo-3(R)-methyl-3,4-dihydro-1H-quinolin-2-one (457mg) in ether (30ml) is added over 10 minutes and the mixture is stirred at 20°C for 2 hours. The mixture is cooled to -5°C and water (5ml) followed by aqueous sodium hydroxide (M, 10ml) are added. The mixture is extracted with ether (4x35ml) and the combined organic extracts are dried (MgSO_4). Evaporation of the solvent gives a colourless oil which solidifies on standing. Chromatography on a column of silicagel using ether:hexane (1:4, by vol.) affords 6-bromo-3(R)-methyl-1,2,3,4-tetrahydro-quinoline [α] $^{20}_D$ = -39.5° (c=0.9, EtOH).

g) Pyridine/sulfur trioxide complex (751mg) is added to a solution of 6-bromo-3(R)-methyl-1,2,3,4-tetrahydro-quinoline (247mg) in pyridine (8ml) at 20°C under nitrogen. The mixture is heated at reflux for 23 hours. After cooling to 20°C, water (20ml) is added and the mixture is extracted with ether (2x10ml). The combined extracts are extracted with water (10ml). The combined aqueous layers are evaporated to obtain a brown oil which is treated with aqueous hydrochloric acid (M, 20ml). The off-white precipitate is collected by filtration and dried in vacuo overnight (NaOH pellets) to give 6-bromo-3(R)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid as an off-white solid which is sufficiently pure for use in the next step.

h) 6-Bromo-3(R)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (177mg) is suspended in DMID (5ml) and treated with pyridine (132 μl) at 20°C under nitrogen to give a solution to which is added phosphoryl chloride (200 μl). The mixture is stirred at 20°C for 3 hours and then poured into ethyl acetate (20ml) which is extracted with water (2x10ml). The combined aqueous layers are back extracted with ethyl acetate (10ml). The combined organic extracts are washed with brine (10ml), dried (MgSO_4) and evaporated to give 6-bromo-3(R)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride as a yellow oil which contains a little DMID. The product is suitable for immediate use.

INTERMEDIATE 1-6

Analogously as described for Intermediate 1-2a-d but using diethylmalonic acid in place of dimethylmalonic acid is prepared 6-chloro-3,3-diethyl-1,2,3,4-tetrahydro-quinoline sulfonic acid, which is converted to 3,3-diethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride as described for Intermediate 1-3 (Method 2).

INTERMEDIATE 1-7

a) Dimethylmalonic acid (1.32g) is dissolved in THF (10ml), thionyl chloride (0.88ml) is added and the mixture is heated at reflux for 2 hours and then cooled to 0°C. A solution of 4-amino-benzoic acid ethyl ester (3.37g) in ether (60ml) is added dropwise between 0°C and 10°C during 60 minutes. The suspension is stirred for 1.5 hours at 0°C and then overnight at room temperature. The suspension is extracted with portions (3x30ml) of ethyl acetate. The combined organic layers are washed with water (30ml), dried (MgSO₄) and evaporated to give a brown residue which is purified by flash chromatography on a column of silicagel eluting with dichloromethane and then dichloromethane:methanol (4:1, by vol.) to give brownish crystals of 4-(2-carboxy-2-methyl-propionylamino)-benzoic acid ethyl ester.

b) Phosphorus pentoxide (16.7g) is dissolved in methane sulphonic acid (261ml) and the solution heated to 70°C. 4-(2-Carboxy-2-methyl-propionylamino)-benzoic acid ethyl ester (58.3g) is added in one portion and the solution is stirred for 24 hours at 70°C. The solution is poured into water (1l) and extracted with portions (3l) of ethyl acetate (2x). The combined organic layers are washed with water (2x500ml), dried (MgSO₄) and evaporated. The residue is dried in vacuo (P₂O₅) overnight. The brown residue is triturated with chloroform (1l), the suspension is filtered and the solid washed with chloroform. This is dried overnight in vacuo to give 3,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid as a cream solid. The residue obtained by evaporation of the mother liquor is dissolved in chloroform (250ml), hexane (2l) is added and the suspension stirred, filtered and the solid washed with hexane. The filtrate is evaporated and the procedure is repeated twice. The combined crops of 3,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester are dried in vacuo.

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The recovered 3,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid (20g) is dissolved in dichloromethane (200ml) and ethanol (15ml), DMAP (7.86g) and DCC (19.4g) are added. The mixture is stirred at room temperature for 12 hours and filtered. The filtrate is washed with portions (100ml) of aqueous hydrochloric acid (2M, 2x), saturated aqueous sodium bicarbonate (3x) and brine, dried (MgSO_4) and evaporated. The residue is purified by flash chromatography on a column of silicagel using dichloromethane:ethyl acetate (9:1, by vol.) as eluate to afford 3,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester as a white solid.

c) 3,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester (10g) is dissolved in ethanol (250ml), 10% palladium on charcoal (2g) is added and the mixture is hydrogenated (1 bar) at room temperature for four days. After removal of the catalyst, evaporation of the filtrate affords white crystals of 3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester.

Alternatively: 3,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-6-carboxylic acid ethyl ester (3.52g) is dissolved in trifluoroacetic acid (100ml) and trimethylsilane (5.6ml) is added. The mixture is heated under nitrogen at 60°C for 6 hours, cooled and poured cautiously into a mixture of saturated aqueous potassium carbonate (20ml) and ice (20ml). The mixture is extracted with portions (3x20ml) of ethyl acetate, the combined extracts are washed with brine (20ml), dried (MgSO_4) and solvent evaporated to give 3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester as an oil which crystallises on trituration with hexane at 4°C.

d) 3,3-Dimethyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester (8.2g) is dissolved in THF (450ml), Lawesson's reagent (13.42g) is added and the mixture heated at reflux for 5.5 hours. The mixture is cooled and evaporated to dryness. The residue is purified by elution with chloroform from a pad (12x19cm diameter) of silicagel to give crystals which are recrystallised from chloroform:hexane to give 3,3-dimethyl-2-thioxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester. Further pure product is obtained by extraction of the silica pad and by work up of the mother liquors.

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Alternatively: 3,3-Dimethyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester (14.4g) is dissolved in dioxan (418ml) and heated to 100°C with vigorous stirring. Phosphorus pentasulfide (11.8g) is added and the mixture is heated for 3 hours and then cooled. The supernatant liquid is collected by decantation and dried. The residue is slurried in dichloromethane (25ml) and applied to a pad (25x15cm diameter) of silicagel which is eluted with hexane:dichloromethane (1:1, by vol., 8.5l) and then dichloromethane (8l) to give 3,3-dimethyl-2-thioxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester as a solid.

e) 3,3-Dimethyl-2-thioxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester (6.25g) is dissolved in THF (100ml), methyl iodide (1.62g) is added and the solution cooled to 0-5°C. Potassium .tert.-butoxide (2.93g) is dissolved in THF (400ml) and the solution added dropwise at 0-5°C during 30 minutes. Further potassium .tert.-butoxide (0.7g) dissolved in THF (12ml) and methyl iodide (80.1) are added dropwise and the mixture stirred for 150 minutes (0-5°C) until all the starting material is consumed. The mixture is poured into ice-water (2l) and extracted with portions (2x250ml) of ethyl acetate. The combined organic layers are washed with portions (25ml) of brine, dried (MgSO₄) and evaporated to give a yellow oil which is purified by flash chromatography on a column of silicagel using dichloromethane as eluant to give 3,3-dimethyl-2-methylsulfanyl-3,4-dihydro-quinoline-6-carboxylic acid ethyl ester as a yellowish oil which crystallises on storage.

f) 3,3-Dimethyl-2-methylsulfanyl-3,4-dihydro-quinoline-6-carboxylic acid ethyl ester (275mg) is dissolved in methanol (10ml) and the solution cooled to 15°C. Sodium cyanoborohydride (124.5mg) is added in one portion and aqueous hydrochloric acid in ethanol (6.8M) is added dropwise to pH 3 at a temperature of 15-20°C. The solution is stirred for 20 minutes, evaporated and the residue extracted with portions (2x20ml) of ethyl acetate. The combined extracts are washed with portions (2x20ml) of saturated aqueous sodium bicarbonate and brine, dried (MgSO₄) and evaporated to give yellowish crystals which are purified by flash chromatography on a column of silicagel eluting with dichloromethane to give 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester as white crystals.

g) 3,3-Dimethyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester (12.4g) is dissolved in dry THF (500ml), cooled to 0°C and borane:methylsulfide complex (6.35ml) is added dropwise with stirring which is continued for 30 minutes at 0°C and then at 20°C for 16 hours. Methanol is added dropwise with caution until excess of reagent is destroyed and solvents are removed by rotary evaporation. Portions of methanol (3x30ml) are distilled from the residue by rotary evaporation and the resulting oil is crystallised from ethyl acetate:hexane to give 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester as white crystals, m.p. 79-80°C.

h) 3,3-Dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester (3.06g) is dissolved in pyridine (120ml), pyridine/sulfur trioxide complex (10.5g) is added and the mixture heated at reflux for 2 hours. The mixture is cooled and evaporated to dryness and the residue extracted with portions of ethyl acetate (2x10ml) and water (3x25ml). The combined water extracts are evaporated and the residue dried in vacuo overnight. Cold aqueous hydrochloric acid (M) is added to the residue, the crystals of 6-ethoxycarbonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid are filtered off and washed with a little cold acid. A further crop of product is obtained from the liquors by evaporation and washing of the residue with cold acid.

i) 6-Ethoxycarbonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (1.6g) is dissolved in DMID (12ml), pyridine (0.76ml) and phosphoryl chloride (0.6ml) are added and the solution is stirred for 40 minutes. The mixture is added to ice-water (400ml) and the solution extracted with portions (3x200ml) of ethyl acetate:ether (1:1, by vol). The combined extracts are dried (MgSO₄) and evaporated to give a residue which contains a little DMID. Repeat partition and work-up gives 8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester as yellow crystals.

INTERMEDIATE 1-8

a) 3,6-Dimethyl-quinoline (200mg) is dissolved in ethanol (7ml) and Nishimura's catalyst (200mg) is added. The suspension is stirred under an atmosphere of hydrogen for 20 hours at 20°C and 1 bar pressure. The catalyst is removed by filtration through Celite, the solvent evaporated and the residue purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (2:1, by vol.) as eluant to give 3(RS),6-dimethyl-1,2,3,4-tetrahydro-quinoline as a white solid.

b) 3(RS),6-Dimethyl-1,2,3,4-tetrahydro-quinoline (130mg) and pyridine/sulfur trioxide complex (256mg) are dissolved in dry toluene and the mixture is heated at reflux for 30 minutes. The solid reaction product is dissolved in aqueous ammonia (M, 5ml) and the solution is washed with ethyl acetate (2x5ml). The aqueous solution is evaporated to dryness and the residue purified by flash chromatography on a column of silicagel using dichloromethane:methanol (5:1, by vol.) as eluant to give 3(RS),6-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid as a white solid.

c) 3(RS),6-Dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (97mg) is dissolved in DMID (2.5ml) and pyridine (0.6ml) is added. To the stirred mixture is added phosphoryl chloride (0.07ml). The mixture is stirred at 20°C for 30 minutes, diluted with water (10ml) and washed with ethyl acetate:ether (1:2, by vol., 5ml). The organic phase is dried (MgSO₄) and the solvent evaporated. The residue is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:5, by vol.) as eluant to give 3(RS),6-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride as a white solid.

INTERMEDIATE 1-9

a) To a solution of 3-methyl-6-methoxy-quinoline (210mg) in methanol (9ml) is added 10% palladium on charcoal catalyst (25mg). The suspension is stirred under a hydrogen atmosphere (1 bar) for 16 hours at 20°C. The catalyst is removed by filtration through Celite and the solvent removed by evaporation in vacuo. The residue is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (5:1, by vol.) as eluant to give 3(RS)-methyl-6-methoxy-1,2,3,4-tetrahydro-quinoline as an oil.

b) 3(RS)-Methyl-6-methoxy-1,2,3,4-tetrahydro-quinoline (310mg) is dissolved in toluene (20ml) and pyridine/sulfur trioxide complex (556mg) is added. The mixture is heated to 95°C for 1 hour, diluted with ethyl acetate (30ml) and washed with dilute aqueous ammonia (3x10ml). The aqueous extracts are evaporated to dryness and the resulting solid purified by flash chromatography on a column of silicagel using dichloromethane:methanol (5:1, by vol.) as eluant to give 3(RS)-methyl-6-methoxy-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid as a white solid.

c) 3(RS)-Methyl-6-methoxy-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (357mg) is dissolved in a mixture of pyridine (0.22ml) and DMID (2ml), cooled to 0°C and treated with phosphoryl chloride (0.25ml) added slowly in portions. The mixture is allowed to warm to 20°C and is stirred for 40 minutes. The mixture is diluted with ethyl acetate:ether (1:1, by vol., 20ml) and washed with water (2x10ml). The organic phase is dried (MgSO₄) and the solvent evaporated in vacuo to give crude 3(RS)-methyl-6-methoxy-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride as a yellow oil which is suitable for immediate use.

INTERMEDIATE 1-10

a) Dimethylmalonic acid (8.84g) is dissolved in dry THF (100ml) under an atmosphere of nitrogen. Thionyl chloride (5.94ml) is added and the mixture is heated to reflux for 2 hours, cooled to 0°C and (4-amino-phenyl)-acetic acid ethyl ester (24g) in ether (300ml) is added dropwise over 1 hour with the temperature below 10°C. The mixture is stirred at room temperature for 2 hours and poured into water (250ml) and the solution extracted with ethyl acetate (2x250ml). The combined extracts are dried (MgSO₄), the solvents evaporated and the residue of crude N-(4-ethoxycarbonylmethyl-phenyl)-2,2-dimethyl-malonamic acid is held in vacuo (NaOH pellets).

b) N-(4-Ethoxycarbonylmethyl-phenyl)-2,2-dimethyl-malonamic acid (10g) and phosphorous pentoxide (5.4g) are dissolved in methane sulfonic acid (75ml) and heated to 70°C with stirring for 3 hours. The reaction mixture is cooled to 20°C and iced water (400ml) is added slowly with stirring. The aqueous phase is extracted with ethyl acetate (3x300ml) and the combined extracts are dried (MgSO₄) and evaporated to a black tar which dissolved in ethyl acetate (200ml) and the solution extracted with saturated aqueous sodium bicarbonate (2x200ml). The combined aqueous extracts are adjusted with aqueous hydrochloric acid (2M) to pH3 and extracted with ethyl acetate (3x200ml). The combined ethyl acetate fractions are dried (MgSO₄) and the residue recrystallised (3x) from ethyl acetate/hexane to give 3,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinolin-6-yl)-acetic acid ethyl ester as white crystals.

c) Aluminium chloride (2.81g) is dissolved in dry ether (15ml) and lithium aluminium hydride (M in THF, 26.3ml) is added slowly at room temperature under nitrogen to maintain a gentle reflux. The mixture is stirred for 30 minutes. 3,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinolin-6-yl)-acetic acid ethyl ester (2.9g) is dissolved in dry THF (30ml) and added slowly to maintain a gentle reflux. The mixture is stirred at room temperature for 2 hours, water (68ml) and aqueous sodium hydroxide (M, 34ml) are added cautiously to quench the reaction mixture, ether (30ml) is added and the mixture is stirred at 20°C for 30 minutes. The ether is decanted and the residue is washed with more ether (2x30ml) and decanted. The combined ether phases are dried (MgSO_4) and evaporated to give a yellow oil which is preabsorbed on silicagel and purified by column chromatography using ethyl acetate:hexane (1:2, by vol.) as eluant to give 2-(3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-ethanol as a beige solid.

d) 2-(3,3-Dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-ethanol (880mg), imidazole (642mg) and tert.-butyl-diphenyl-silyl chloride are dissolved in DMF (3ml) and stirred at 20°C for 70 hours. The mixture is diluted with ethyl acetate (10ml) and extracted with aqueous hydrochloric acid (0.1M, 2x20ml). The extracts are back-extracted with ethyl acetate (10ml) and the combined ethyl acetate phases are dried (MgSO_4). The solid product which precipitates out over the MgSO_4 is filtered off. The filtrate is evaporated and the residue is purified by crystallising from ethyl acetate and column chromatography on silicagel using hexane/ethyl acetate (3:1, by vol.) as eluant to yield further 6-[2-(tert.-butyl-diphenyl-silanyloxy)-ethyl]-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline as a white solid.

e) 6-[2-(tert.-Butyl-diphenyl-silanyloxy)-ethyl]-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline (813mg) and pyridine/sulfur trioxide complex (1.17g) in toluene (10ml) is heated at reflux for 3 hours. The mixture is cooled and poured into ice/water (25ml). The solution is extracted with ethyl acetate (3x25ml) and the combined extracts are dried (MgSO_4) and evaporated. The residue is purified by column chromatography on silicagel using methanol:dichloromethane (1:9, by vol.) as eluant to give 6-[2-(tert.-butyl-diphenyl-silanyloxy)-ethyl]-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid as an off-white foam.

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f) 6-[2-(tert.-Butyl-diphenyl-silanyloxy)-ethyl]-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (100mg) is dissolved in DMID (1ml) and pyridine (40•l) and the solution is cooled to 0°C under nitrogen. Phosphoryl chloride (40•l) is added and the mixture is stirred at 20°C for 30 minutes and poured into ethyl acetate (5ml). The solution is extracted with water (2x25ml), the water back-extracted with ethyl acetate (10ml) and the combined organic phases are dried (MgSO₄) and evaporated to give 6-[2-(tert.-butyl-diphenyl-silanyloxy)-ethyl]-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride as a yellow oil which is held in vacuo (NaOH pellets) and is suitable for immediate use.

INTERMEDIATE 1-11

Method 1

a) 2-Aminobenzonitrile (130.3g) in dichloromethane (1.1l) is added with stirring to a solution of potassium carbonate (152.4g) in water (550ml). A solution of 2-bromo-2-methyl propionyl bromide (279.1g) in dichloromethane (300ml) is added dropwise over 1 hour keeping the temperature of the mixture below 25°C and the resulting emulsion is stirred vigorously for 3 hours. The organic phase is separated and the aqueous phase is washed with dichloromethane (220ml). The combined organic phases are rotary evaporated to dryness and the resulting orange crystalline mass of 2-bromo-N-(2-cyano-phenyl)-isobutyramide is dried for 16 hours in vacuo, m.p. 66-69°C.

b) A solution of 2-bromo-N-(2-cyano-phenyl)-isobutyramide (296.1g) in dry THF (1l) is added dropwise over 2 hours to a solution of ethyl magnesium bromide (512.9g) in dry THF (1.2l) under conditions of gentle reflux. The resulting mixture is stirred and heated at reflux for 16 hours and cooled. The suspension is added with stirring to a mixture of aqueous hydrochloric acid (1.1l) and crushed ice (1kg) and the mixture is stirred for 1 hour, allowing it to come to room temperature. The mixture is extracted with ethyl acetate (2x1l) and the combined extracts are washed with brine (1l), dried (Na₂SO₄) and evaporated to give an orange crystalline mass which is washed by suspension in 2-methoxy-2-methyl-propane (250ml), filtration and washing with 2-methoxy-2-methyl-propane (100ml). The liquors yield further product on evaporation and trituration with cold 2-methoxy-2-methyl-propane.

The combined yellow crystals are dried for 16 hours at 50°C to give 3,3-dimethyl-1H-quinoline-2,4-dione, m.p. 157-161°C.

c) 3,3-Dimethyl-1H-quinoline-2,4-dione (126.5g) dissolved in dry THF (730ml) is added dropwise over 2.5 hours to an ice-cold preformed mixture of lithium aluminium hydride (76.2g) and aluminium trichloride (89.2g) in dry THF (1.46l) and the mixture is stirred for a further 2 hours at 0°C. A mixture of water (90ml) and THF (150ml) is added cautiously to the well-stirred solution under cooling, THF (150ml) is added to the thick suspension followed by aqueous sodium hydroxide (15% w/v, 90ml) and water (270ml) and the mixture is stirred at room temperature for 16 hours. Solids are removed by filtration and washed with THF (1.5l) and the combined filtrates are evaporated to dryness. The residue is dissolved in 2-methoxy-2-methyl-propane (300ml), washed with brine (100ml), dried (Na_2SO_4) and the solution evaporated to give crude 3,3-dimethyl-1,2,3,4-tetrahydroquinoline which is purified by distillation (60-65°C/0.4mbar) to give a light yellow liquid.

d) 3,3-Dimethyl-1,2,3,4-tetrahydroquinoline (93.3g) is dissolved in a mixture of dichloromethane (1.65l) and methanol (550ml) and cooled to 5°C. BTMA. ICl_2 (211.3g) and potassium carbonate (75.2g) are added and the suspension is stirred at 5°C for 1.5 hours. The solids are collected by filtration, washed with dichloromethane (250ml) and the combined filtrates dried by rotary evaporation. The residue is dissolved in a mixture of 2-methoxy-2-methyl-propane (2l) and water (1l), the organic phase is collected and the aqueous phase is extracted with a second portion (300ml) of the ether. The combined organic phases are washed with aqueous sodium thiosulfate (1% w/v, 1l), water (500ml), brine (500ml), dried (Na_2SO_4) and the solution evaporated to a volume of 2l. The solution is saturated with hydrogen chloride and the crystalline material is collected by filtration, washed with 2-methoxy-2-methyl-propane (500ml) and dried in vacuo to give 6-iodo-3,3-dimethyl-1,2,3,4-tetrahydroquinoline hydrochloride as yellow crystals, m.p. 145-7°C.

e) 6-Iodo-3,3-dimethyl-1,2,3,4-tetrahydroquinoline hydrochloride (253.3g) is stirred with dry DMF (1.25l) and sodium bicarbonate (230.4g) is added in portions followed by acrylic acid ethyl ester (117.7g), tetrabutylammonium chloride (231.9g) and palladium(II)acetate (3.5g). The mixture is stirred at 80°C for 2 hours, cooled to room temperature and dried by rotary evaporation.

The residue is shaken with 2-methoxy-2-methyl-propane (1.5l) and water (500ml), solids removed by filtration and the separated aqueous phase washed with a further portion (500ml) of the ether. The combined organic phases are washed with portions (500ml) of water and brine, dried (Na_2SO_4) and the solution evaporated to dryness to give 3-(3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-acrylic acid ethyl ester as a light brown oil suitable for immediate use.

f) 3-(3,3-Dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-acrylic acid ethyl ester (210g) is dissolved in ethanol (2l) and hydrogenated (1 bar) in the presence of 10% palladium on charcoal (21g) for 10 hours at room temperature. Removal of the catalyst and solvent affords 3-(3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester which is purified by vacuum distillation (141-4°C/0.02mbar).

g) 3-(3,3-Dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (206g) is dissolved in DMF (2l) and DMF/sulfur trioxide complex (133g) is added with stirring. The mixture is heated to 80°C with stirring for 1 hour and rotary evaporated to dryness. The residue is dissolved under reflux in butan-2-one (500ml) and 2-methoxy-2-methyl-propane (1l) is added. After cooling to 5°C, the crystals are recovered by filtration, washed with butan-2-one:2-methoxy-2-methyl-propane (1:2, by vol., 200ml) and the ether (250ml) and dried at 50°C in vacuo for 16 hours to give 6-(2-ethoxycarbonyl-ethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid as beige crystals, m.p. 162-5°C.

h) Analogously as described for foregoing Intermediates but using 6-(2-ethoxycarbonyl-ethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid is prepared 3-(8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester, which crystallises on storage in vacuo. $[\text{M}+\text{H}]^+ = 359.9, 361.8$.

Method 2

Analogously as described for Intermediate 1-7a-b but using 3-(4-amino-phenyl)-acrylic acid ethyl ester in place of 4-aminobenzoic acid ethyl ester is prepared 3-(3,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinolin-6-yl)-acrylic acid ethyl ester which is hydrogenated as described for Intermediate 1-7c but using acetic acid:methanol (1:4, by vol.) in place of ethanol as solvent to afford 3-(3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester. This is treated as described for Intermediate 1-7d-i to yield 3-(8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a pale yellow solid identical to that obtained by Method 1 of this example.

Alternatively:

- a) 3-(3,3-Dimethyl-2,4,-dioxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (1.01g) is dissolved in a mixture of THF (20ml) and ethanol (40ml) and hydrogenated (1 bar) in the presence of 10% palladium on charcoal (0.11g) at 20°C for 3 hours. After removal of catalyst and solvents, the residue is purified by flash chromatography on a column of silicagel using ethyl acetate as eluant to give 3-(4(RS)-hydroxy-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a colourless oil.
- b) 3-(4(RS)-Hydroxy-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (0.9g), DMAP (0.1g) and triethylamine (0.57m) are dissolved in dichloromethane (20ml) and acetic anhydride (0.32ml) is added. The solution is stirred for 3 hours, evaporated to dryness by rotary evaporation and the residue purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (7:3, by vol.) as eluant to give 3-(4(RS)-acetoxy-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a colourless oil.
- c) 3-(4(RS)-Acetoxy-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (0.8g) is dissolved in ethanol (30ml) and palladium oxide (0.2g) is added. The mixture is hydrogenated at 20°C for 3 days. Removal of catalyst and solvent gives a residue which is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:1, by vol.) as eluant to give 3-(3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a colourless oil which crystallises on storage.

This is treated as described for Intermediate 1-7d-i to yield 3-(8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester identical to that obtained by Method 1 of this example.

Method 3

Analogously as described for Intermediate 1-7a-b but using 3-(4-amino-phenyl)-propionic acid ethyl ester in place of 4-aminobenzoic acid ethyl ester is prepared 3-(3,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester which is hydrogenated as described for Intermediate 1-7c but using acetic acid:methanol (1:4, by vol.) in place of ethanol as solvent to afford 3-(3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester. This is treated as described for Intermediate 1-7d-i to yield 3-(8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a pale yellow solid identical to that obtained by Method 1 of this example.

INTERMEDIATE 1-12

Analogously as described for Intermediate 1-11 (method 2) but using diethylmalonic acid in place of dimethylmalonic acid is obtained 3-(8-chlorosulfonyl-3,3-diethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a pale yellow oil.

INTERMEDIATE 1-13

a) Analogously as described for Intermediate 1-2a-d but using 4-fluoroaniline in place of 4-chloroaniline is prepared 6-fluoro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid. 6-Fluoro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline is obtained crystalline on purification by flash chromatography on a column of silicagel using hexane:ether (1:1, by vol.) as eluant. 6-Fluoro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (4:1, by vol.) as eluant.

b) Analogously as described for Intermediate 1-7i but using 6-fluoro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid in place of 6-fluoro-3,3-dimethyl-6-ethoxycarbonyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid is prepared 6-fluoro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride.

INTERMEDIATE 1-14

- a) A solution of 3,4-dihydro-1H-quinolin-2-one (11g) in dry THF (50ml) is added at 0°C to a solution of LDA in hexane (1.5M, 100ml) and a further portion (450ml) of cold, dry THF is added. The solution is allowed to warm to room temperature and is stirred for 2 hours and the solution is cooled to -78°C. Ethyl iodide (6ml) is added and the stirred solution is allowed to warm to room temperature, diluted with ethyl acetate (600ml) and washed with water (2x500ml). The combined water washings are back-extracted with ethyl acetate (2x100ml) and the combined ethyl acetate fractions are dried (MgSO₄) and evaporated to dryness to give 3(RS)-ethyl-3,4-dihydro-1H-quinolin-2-one as a pale yellow solid.
- b) 3(RS)-Ethyl-3,4-dihydro-1H-quinolin-2-one (11g) is dissolved in dry THF (200ml) and BH₃.DMS complex (18.8ml) is added at 0°C. The mixture is stirred at 20°C for 72 hours and then heated at reflux for 2 hours. Methanol is added cautiously to quench the reaction mixture and solvents are removed by rotary evaporation. The residue is purified by chromatography on a column of silicagel which is eluted with hexane:ether (8:1, by vol.) to give 3(RS)-ethyl-1,2,3,4-tetrahydro-quinoline as a colourless oil.
- c) 3(RS)-Ethyl-1,2,3,4-tetrahydro-quinoline (5g) is dissolved in dry dichloromethane (135ml) and BTMA.ICl₂ (10.8g) is added. Calcium carbonate (4g) and methanol (50ml) are added and the resultant slurry is stirred at 20°C for 16 hours, diluted with dichloromethane (100ml) and washed with portions (2x100ml) of 5% (w/v) aqueous sodium bisulphite. The organic phase is dried (MgSO₄) and evaporated to dryness to give 3(RS)-ethyl-6-iodo-1,2,3,4-tetrahydro-quinoline as a colourless oil which solidifies on storage.
- d) 3(RS)-Ethyl-6-iodo-1,2,3,4-tetrahydro-quinoline (7.7g), acrylic acid ethyl ester (4.34ml), triethylamine (5.5ml) and tri-(ortho-tolyl)-phosphine (2.43g) are dissolved in dry DMF (15ml), palladium(II)acetate (0.6g) is added and the mixture is heated at 100°C for 16 hours. Ethyl acetate (150ml) is added to the cooled solution which is washed with portions (2x200ml) of water, the organic phase is dried (MgSO₄) and rotary evaporated.

The residue is purified by chromatography on a column of silicagel using hexane:ether (4:1, by vol.) as eluant to afford 3-(3(RS)-ethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-acrylic acid ethyl ester as a yellow oil.

e) 3-(3(RS)-Ethyl-1,2,3,4-tetrahydro-quinoliny)-6-acrylic acid ethyl ester (3.3g) is dissolved in ethanol (100ml) and palladium on charcoal (5%, 330mg) is added. The mixture is hydrogenated at 1 bar and 20°C for 5 hours. The catalyst is removed by filtration and the solution evaporated to dryness to give 3-(3(RS)-ethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a colourless oil.

f) Analogously as described for Intermediate 1-7h-i but using 3-(3(RS)-ethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester is obtained 3-(8-chlorosulfonyl-3(RS)-ethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a light yellow oil.

INTERMEDIATE 1-15

Analogously as described for Intermediate 1-14 but using propyl iodide in place of ethyl iodide is obtained 3-(8-chlorosulfonyl-3(RS)-propyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester.

INTERMEDIATE 1-16

Analogously as described for Intermediate 1-14 but using isopropyl iodide in place of ethyl iodide is obtained 3-(8-chlorosulfonyl-3(RS)-isopropyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester.

INTERMEDIATE 1-17

Analogously as described for Intermediate 1-14 but using butyl iodide in place of ethyl iodide is obtained 3-(8-chlorosulfonyl-3(RS)-butyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester.

INTERMEDIATE 1-18

Analogously as described for Intermediate 1-14 but using isobutyl iodide in place of ethyl iodide is obtained 3-(8-chlorosulfonyl-3(RS)-isobutyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester.

INTERMEDIATE 1-19

Analogously as described for Intermediate 1-14 but using methyl iodide in place of ethyl iodide is obtained 3-(8-chlorosulfonyl-3(RS)-methyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester.

INTERMEDIATE 1-20

- a) Analogously as described for Intermediate 1-7a-b but using 5-amino-2-chlorobenzoic acid methyl ester in place of 4-aminobenzoic acid ethyl ester is prepared 6-chloro-3,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoline-5-carboxylic acid methyl ester obtained as a waxy solid isolated by chromatography on a column of silicagel using ethyl acetate:hexane (2:3, by vol.) as eluant.
- b) 6-Chloro-3,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoline-5-carboxylic acid methyl ester (1.18g) is dissolved in trifluoroacetic acid (3.6ml), stirred under nitrogen at room temperature and trimethylsilane (1.5ml) is added. The mixture is heated at 55-60°C for 45 hours with addition of further silane at 25 hours (1.2ml) and 42 hours (1.2ml). The cooled mixture is poured into a mixture of saturated aqueous sodium bicarbonate (30ml) and ice (20g), the mixture is extracted with dichloromethane (4x25ml), the combined extracts are dried (MgSO₄) and solvent evaporated to give material which is purified by chromatography on a column of silicagel using ethyl acetate:hexane (2:3, by vol.) to give 6-chloro-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinoline-5-carboxylic acid methyl ester as a white solid.

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c) Analogously as described for Intermediate 1-7g-i but using 6-chloro-3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinoline-5-carboxylic acid methyl ester in place of 3,3-dimethyl-2-oxo-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester is prepared 6-chloro-8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-5-carboxylic acid methyl ester as a light yellow oil suitable for immediate use.

INTERMEDIATE 1-21

a) 6-Chloro-5-methoxycarbonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (279mg) is dissolved in methanol (15ml) and triethylamine (0.475ml) and is hydrogenated (1 bar) in the presence of 10% palladium on charcoal (98mg) for 25 hours at 20°C. Removal of the catalyst and solvent gives an oil which is purified by chromatography on a column of silicagel using methanol:dichloromethane (1:4, by vol.) to give 5-methoxycarbonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid as an off-white solid.

b) Analogously as described for Intermediate 1-7i but using 5-methoxycarbonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid in place of 6-ethoxycarbonyl-3,3-dimethyl-1,2,3,4-tetrahydroquinoline-8-sulfonic acid is prepared 8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydroquinoline-5-carboxylic acid methyl ester as a yellow oil suitable for immediate use.

INTERMEDIATE 1-22

a) (1,2,3,4-Tetrahydro-quinolin-3(RS)-yl)-methanol (1.79g) is dissolved in dry THF (10ml) and sodium hydride dispersion (60%, 442mg) is added. The suspension is stirred at room temperature for 20 minutes, methyl iodide (0.68ml) is added and the mixture is stirred for 4 hours. Water (1ml) is added followed by ether (20ml) and the mixture is washed with water (20ml). The separated organic phase is dried (MgSO₄) and the solvent evaporated to give a residue which is purified by flash chromatography on a column of silicagel using hexane:ether (1:1, by vol.) as eluant to give 3(RS)-methoxymethyl-1,2,3,4-tetrahydro-quinoline as a colourless oil.

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b) Analogously as described for Intermediate 1-14c-f but using 3(RS)-methoxymethyl-1,2,3,4-tetrahydro-quinoline in place of 3(RS)-ethyl-1,2,3,4-tetrahydro-quinoline is prepared 3-(8-chlorosulfonyl-3(RS)-methoxymethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a yellow oil suitable for immediate use.

INTERMEDIATE 1-23

a) 3-(3,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (560mg) is dissolved in dry THF (10ml) and borane-dimethylsulfide complex (10M, 0.4ml) is added. The mixture is stirred under nitrogen at room temperature for 30 minutes and methanol (10ml) is added slowly. The mixture is stirred for 15 minutes and solvents are removed by rotary evaporation to give a yellow oil which is purified by chromatography on a column of silicagel using ethyl acetate:dichloromethane (1:19 to 1:4, by vol.) as eluant to give 3-(3,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester and 3-(3,3-dimethyl-4(RS)-hydroxy-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester separately as colourless oils.

b) 3-(3,3-Dimethyl-4-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (112mg) is dissolved in dry DMF (2.5ml) and sulfur trioxide/DMF complex (260mg) is added. The mixture is heated at 100°C for 1.5 hours, cooled to room temperature and rotary evaporated to dryness to give a brown oil which is purified by flash chromatography on a column of silicagel using methanol:dichloromethane (1:9, by vol.) as eluant to give 6-(2-ethoxycarbonyl-ethyl)-3,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid as a yellow solid.

c) 6-(2-Ethoxycarbonyl-ethyl)-3,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (120mg) is dissolved in DMID (2.5ml) under nitrogen and pyridine (0.08ml) and phosphoryl chloride (0.13ml) are added. The mixture is stirred at room temperature for 4 hours, poured into ethyl acetate (20ml) and the solution is washed with ice-water (10ml). The separated aqueous phase is washed with ethyl acetate (10ml) and the combined organic phases are dried (MgSO₄) and evaporated to give 3-(8-chlorosulfonyl-3,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a yellow oil, suitable for immediate use.

INTERMEDIATE 1-24

- a) (1,2,3,4-Tetrahydro-quinolin-3(RS)-yl)-methanol is converted by a standard reaction using benzyl chloroformate to 3(RS)-hydroxymethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester.
- b) 3(RS)-Hydroxymethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (3.2g) and imidazole (1.61g) are dissolved in DMF (20ml) and tert.-butyldiphenylsilyl chloride (3.79ml) is added. The mixture is stirred for 40 hours at room temperature and aqueous hydrochloric acid (100ml, 2M) is added. The mixture is extracted with portions (2x50ml) of ethyl acetate, the combined extracts are washed with water (50ml), dried (MgSO₄) and the solvents removed by rotary evaporation to give a yellow oil which is purified by chromatography on a column of silicagel using hexane:ether (8:1, by vol.) as eluant to give 3(RS)-(tert.-butyl-diphenyl-silanyloxymethyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester as a colourless oil.
- c) 3(RS)-(tert.-Butyl-diphenyl-silanyloxymethyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (3.81g) is dissolved in a mixture of ethanol (20ml) and methanol (20ml) and hydrogenated (1 bar) for 6 hours at room temperature in the presence of 10% palladium on charcoal (381mg) to give, after removal of the catalyst and evaporation of the solvents, 3(RS)-(tert.-butyl-diphenyl-silanyloxymethyl)-1,2,3,4-tetrahydro-quinoline as a colourless oil.
- d) Analogously as described for Intermediate 1-14c-f but starting from 3(RS)-(tert.-butyl-diphenyl-silanyloxymethyl)-1,2,3,4-tetrahydro-quinoline in place of 3(RS)-ethyl-1,2,3,4-tetrahydro-quinoline is prepared 3-[3(RS)-(tert.-butyl-diphenyl-silanyloxymethyl)-8-chlorosulfonyl-1,2,3,4-tetrahydro-quinolin-6-yl]-propionic acid ethyl ester. It is obtained as a yellow oil suitable for immediate use.

INTERMEDIATE 1-25

- a) 1,2,3,4-tetrahydro-quinoline-3(RS)-carboxylic acid is converted by a standard procedure using benzyl chloroformate to 3,4-dihydro-2H-quinoline-1,3(RS)-dicarboxylic acid 1-benzyl ester.

- b) 3,4-Dihydro-2H-quinoline-1,3(RS)-dicarboxylic acid 1-benzyl ester (6.15g), PyBOP (15.56g) and Huenig Base (13ml) are dissolved in dichloromethane (200ml) and the mixture is stirred for 10 minutes at 20°C. N,O-Dimethylhydroxylamine hydrochloride (2.88g) is added and the mixture is stirred for a further two hours. The solution is diluted with dichloromethane (200ml), washed with aqueous hydrochloric acid (2M, 200ml), dried (MgSO₄) and solvent removed by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (4:1, by vol.) as eluant to give 3(RS)-(methoxymethylcarbamoyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester.
- c) 3(RS)-(Methoxy-methyl-carbamoyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (6.795g) is dissolved in dry THF (100ml) and methylmagnesium bromide 1.4M in THF, 21.28ml) is added. The mixture is stirred for 2 hours at 20°C, water (5ml) is added followed by ethyl acetate (100ml) and the solution is washed with aqueous hydrochloric acid (M, 100ml). The organic phase is dried (MgSO₄) and the solvent removed by rotary evaporation to give a residue which is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:3, by vol.) as eluant to give 3(RS)-acetyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester.
- d) 3(RS)-Acetyl-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (5.5g) is dissolved in dichloromethane (50ml) and 3-chloroperoxybenzoic acid (50%, 12.2g) is added. The mixture is stirred at 20°C for 24 hours, a further portion (15g) of 3-chloroperoxybenzoic acid is added and the mixture is stirred for a further 24 hours. Aqueous sodium sulfite (100 ml, 10% w/v) is added followed by dichloromethane (50ml) and the solution is stirred vigorously for 45 minutes. The mixture is washed with portions (3x10ml) of aqueous sodium sulfite (10% w/v), the organic phase dried (MgSO₄) and the solvent removed by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:4, by vol.) as eluant to give 3(RS)-acetoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester as a colourless oil.
- e) 3(RS)-Acetoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester is saponified as described for Example 225c and 3(RS)-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester is recovered by extraction with ethyl acetate. Storage of the oil obtained yields a cream solid.

f) 3(RS)-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.85g) is dissolved in DMF (40ml) and ethyl iodide (8ml) is added. The stirred mixture is cooled to 0°C and sodium hydride suspension (60% w/v, 0.8g) is added. The mixture is stirred at 20°C for 2 hours, diluted with ether (100ml) and washed with portions (2x100ml) of water. The organic phase is dried (MgSO₄), the solvent removed by rotary evaporation and the residue obtained is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:5, by vol.) as eluant to give 3(RS)-ethoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester as a colourless oil.

g) 3(RS)-Ethoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid benzyl ester (2.81g) is dissolved in ethanol (150ml) and hydrogenated (1 bar) in the presence of 10% (w/w) palladium on charcoal for 5 hours at 20°C to give, after removal of the catalyst and solvent, 3(RS)-ethoxy-3,4-dihydro-2H-quinoline as a colourless oil.

h) Analogously as described for Example 1-14c-f but using 3(RS)-ethoxy-1,2,3,4-tetrahydro-quinoline in place of 3(RS)-ethyl-1,2,3,4-tetrahydro-quinoline is prepared 3-(8-chlorosulfonyl-3(RS)-ethoxy-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a light yellow oil.

INTERMEDIATE 1-26

Analogously as described for Intermediate 1-7i but using 1,2,3,4-tetrahydro-quinoline-8-sulfonic acid in place of 6-ethoxycarbonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid is prepared 1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride which is obtained as a yellow oil.

INTERMEDIATE 1-27

Analogously as described for Intermediate 1-14c-f but using 1,2,3,4-tetrahydro-quinoline in place of 3(RS)-ethyl-1,2,3,4-tetrahydro-quinoline is prepared 3-(8-chlorosulfonyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester which is obtained as a yellow oil.

INTERMEDIATE 1-28

Analogously as described for Intermediate 1-10 but using diethylmalonic acid in place of dimethylmalonic acid is prepared 6-[2-(tert.-butyl-diphenyl-silanyloxy)-ethyl]-3,3-diethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride as a yellow oil. $[M+H] = 570.2, 572.2$.

INTERMEDIATE 1-29

Analogously as described for Intermediate 1-7 but using diethylmalonic acid in place of dimethylmalonic acid is prepared 8-chlorosulfonyl-3,3-diethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester as a white solid.

INTERMEDIATE 2-1

Piperidin-4-ylmethanol (7g) is suspended in acetic acid (15ml) and the mixture is cooled in ice. Hydrogen chloride gas is passed through the mixture until all the material has dissolved. The reaction mixture is heated at reflux for 30 minutes. The solvent is removed by evaporation and the oil obtained is dried (NaOH pellets) in vacuo. The resulting solid is recrystallised from ethanol to yield acetic acid piperidin-4-ylmethyl ester hydrochloride as a white solid, m.p. 164-165°C. (Found: C, 48.85; H, 8.01; N, 7.26; Cl, 17.89. $C_8H_{16}NO_2Cl \cdot 0.2H_2O$ requires C, 48.71; H, 8.38; N, 7.1; Cl, 17.97%).

INTERMEDIATE 2-2

Propionic acid piperidin-4-ylmethyl ester hydrochloride is prepared as described for Intermediate 2-1 but using propionic acid in place of acetic acid, m.p. 168-9°C. (Found: C, 52.05; H, 8.89; N, 6.86. $C_9H_{18}NO_2Cl$ requires C, 52.04; H, 8.74; N, 6.74%).

INTERMEDIATE 2-3

Piperidin-4-yl-ethanol (50g) is dissolved in acetic acid (1l) and cooled in ice. Hydrogen chloride gas is passed through the solution for 2 hours, the reaction mixture is sealed and kept at 20°C for 16 hours and finally heated at reflux for 30 minutes. After cooling, the solvent is removed by evaporation and the residue held in vacuo (NaOH pellets) to give an oil which is stirred with ether (1l) to give crystals, m.p. 80-90°C. Recrystallisation from ethyl acetate affords acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride, m.p. 115-7°C. (Found: C, 51.90; H, 8.99; N, 6.64; Cl, 17.19. $C_9H_{18}NO_2Cl$ requires C, 52.04; H, 8.74; N, 6.74; Cl, 17.07%).

INTERMEDIATE 2-4

Analogously as described for Intermediate 2-3 but using propionic acid instead of acetic acid is obtained propionic acid 2-piperidin-4-yl-ethyl ester hydrochloride.

INTERMEDIATE 2-5

a) 4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (29.5g) is dissolved in dry dichloromethane (78.4ml) and carbon tetrachloride (12.4ml) is added. Triphenylphosphine (33.8g) is added in dry dichloromethane (78ml) slowly over 1 hour. The mixture is stirred at 20°C for 3 hours, a further 0.5 eq. of carbon tetrachloride is added and the reaction mixture is stirred at 20°C for 16 hours. Hexane is added to turbidity and the mixture is washed with portions (2x100ml) of saturated aqueous sodium bicarbonate water, brine, dried ($MgSO_4$) and the solvents evaporated to give an oily white solid. This is purified using a pad of silicagel which is eluted with ether:hexane (3:7, by vol.) to afford 4-(2-chloro-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester as a white solid, m.p. 49.5-51°C.

b) 4-(2-Chloro-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (3.5g) is dissolved in saturated hydrogen chloride in acetic acid (28ml) and the solution is stirred for 2 hours at 20°C. The solvents are removed by rotary evaporation at reduced pressure and the residue triturated with dry ether to give 4-(2-chloro-ethyl)-piperidine hydrochloride as a white solid.

INTERMEDIATE 2-6**Method 1**

a) 4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (5.15g) is dissolved in fluorotrichloromethane (15ml) and cooled to -78°C in an atmosphere of dry nitrogen. A solution of DAST (3.55ml) in fluorotrichloromethane (15ml) is added and the mixture is stirred with exclusion of moisture for 10 minutes at -78°C and then allowed to warm to room temperature.

After a further 30 minutes, the mixture is poured into ice-water (30ml) and the organic phase separated, washed with brine (2x10ml), dried (MgSO_4) and the solvent removed by evaporation at reduced pressure to give a residue which is purified by flash chromatography on a column of silicagel using ether:hexane (1:1, by vol.) as eluant. Appropriate fractions are combined and the solvent removed to give 4-(2-fluoro-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester.

b) 4-(2-Fluoro-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (2.2g) is dissolved in saturated hydrogen chloride in acetic acid (12ml) and the solution stirred for 2 hours at 20°C. The solvent is removed by evaporation at reduced pressure and portions of methanol (2x50ml) are evaporated from the residue to give 4-(2-fluoro-ethyl)-piperidine hydrochloride which is held in vacuo (NaOH pellets).

Method 2

4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (6.53g) is dissolved in dichloromethane (29ml) and the solution is heated to 80°C at 2 bar (autoclave). Ishikawa reagent (7.29g) dissolved in dichloromethane (8ml) is added over a period of 1 hour under pressure and the mixture is heated for 1.5 hours at 12 bar at 80°C. The cooled mixture is washed with portions (2x20ml) of 50% brine and 50% brine buffered to pH4-5. The organic phase is dried (Na_2SO_4) and solvent removed by rotary evaporation to give an oil which is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (10:1, by vol.) as eluant to give pure 4-(2-fluoro-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester as a light yellow oil. This is converted to 4-(2-fluoro-ethyl)-piperidine hydrochloride as described in Method 1 above.

Method 3

a) [4-(2-Hydroxy-ethyl)-piperidin-1-yl]-phenyl-methanone (31.5g) is dissolved in dichloromethane (200ml) and pyridine (10.9ml) and methanesulfonyl chloride (11.5ml) are added. The mixture is stirred for 2 hours and the volume reduced to 50ml by evaporation, ethyl acetate (250ml) is added and the solution is washed with portions (250ml) of saturated aqueous sodium bicarbonate and water, the organic phase is dried (MgSO_4) and evaporated to give methanesulfonic acid 2-(1-benzoyl-piperidin-4-yl)-ethyl ester as a waxy solid which is sufficiently pure for use without further purification.

b) Methanesulfonic acid 2-(1-benzoyl-piperidin-4-yl)-ethyl ester (41.5g) is dissolved in acetonitrile (150ml), powdered molecular sieve (4 Angstrom) is added followed by TBAF (1M in THF, 145ml) and the mixture is heated at reflux with exclusion of moisture for 2 hours. The mixture is cooled, filtered and the filtrate washed with saturated aqueous sodium bicarbonate (2x200ml) and brine (200ml), dried (MgSO_4) and the solvent evaporated to give an orange oil. Purification by flash chromatography on a column of silicagel using hexane:ether (1:1, by vol.) and then ether as eluents gives [4-(2-fluoro-ethyl)-piperidin-1-yl]-phenyl-methanone as an oil.

c) [4-(2-Fluoro-ethyl)-piperidin-1-yl]-phenyl-methanone (17.1g) is dissolved in methanol (30ml), aqueous hydrochloric acid (6M, 60ml) is added and the mixture is heated at reflux for 72 hours. Methanol is removed by rotary evaporation and the remaining aqueous solution is washed with ethyl acetate (3x20ml). Solid sodium hydroxide is added to a final pH of 12 and the solution is extracted with ethyl acetate (3x25ml). The combined extracts are dried (MgSO_4) and evaporated to give 4-(2-fluoro-ethyl)-piperidine as a colourless oil after purification by vacuum distillation, b.p. $45^\circ\text{C}/3\text{mm}$.

INTERMEDIATE 2-7

a) Pyridinium chlorochromate (1.41g) is suspended in dry dichloromethane (10ml) and 4-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid (tert.-butyl ester (1.0g) dissolved in dichloromethane (2ml) is added. The mixture is stirred at 20°C for 6 hours, ether (10ml) is added and the mixture is filtered through a pad of Celite. The filtrate is dried by rotary evaporation and the crude product purified by flash chromatography on a column of silicagel using ethyl acetate as eluant to give 4-(2-oxo-ethyl)-piperidine-1-carboxylic acid (tert.-butyl ester).

b) 4-(2-Oxo-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (545mg) is dissolved in dry dichloromethane (2ml) in an atmosphere of nitrogen. DAST (1ml) is added and the reaction mixture is stirred at 20°C for 1 hour and then poured into water (10ml).

The mixture is extracted with dichloromethane (2x10ml), the combined extracts dried (MgSO₄) and the solvent removed by rotary evaporation to give crude product which is purified by flash chromatography on a column of silicagel using hexane:ether (1:1, by vol.) as eluant to give 4-(2,2-difluoro-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester.

c) Using the procedure described for Intermediate 2-6b (Method 1), 4-(2,2-difluoro-ethyl)-piperidine-1-carboxylic acid (tert.-butyl ester is converted to 4-(2,2-difluoro-ethyl)-piperidine hydrochloride which is held in vacuo (NaOH pellets).

INTERMEDIATE 2-8

a) To a solution of 2-piperazin-1-yl-ethanol (15g) and sodium bicarbonate (10.67g) in dioxane/water (1:1, 500ml) is added di-(tert.-butyl dicarbonate (27.66g) in portions at 20°C with stirring for 3 hours. Solvents are removed by rotary evaporation, the residue dissolved in cold 10% aqueous citric acid (100ml) and the solution is extracted with ethyl acetate (3x100ml). The combined extracts are dried (MgSO₄) and evaporated to give 4-(2-hydroxy-ethyl)-piperazine-1-carboxylic acid (tert.-butyl ester as a colourless oil.

b) A solution of DAST (14g) in dry dichloromethane (30ml), cooled to -78°C , is injected by syringe into a solution of 4-(2-hydroxy-ethyl)-piperazine-1-carboxylic acid (tert.-butyl ester) (10g) in dry dichloromethane (170ml) also cooled to -78°C under nitrogen and the mixture is stirred for 1.5 hours. Any excess of DAST is neutralised by pouring the reaction mixture onto ice-water (30ml). After evaporating the reaction mixture to dryness and desiccating over sodium hydroxide pellets, the residue is purified by chromatography on a column of silicagel eluting with ethyl acetate to give pure 4-(2-fluoro-ethyl)-piperazine-1-carboxylic acid tert.-butyl ester as a white solid.

c) A solution of 4-(2-fluoro-ethyl)-piperazine-1-carboxylic acid tert.-butyl ester (3.72g) in hydrogen chloride in acetic acid (M, 48.2ml) is stirred for 2 hours at 20°C . Solvent is removed by rotary evaporation and portions (3x30ml) of ethanol are evaporated from the residue to remove excess of acid. The 1-(2-fluoro-ethyl)-piperazine hydrochloride salt obtained is kept as a white solid in vacuo (NaOH pellets).

INTERMEDIATE 2-9

a) 1-Benzyl-piperazine (974mg) is stirred with finely-powdered potassium iodide (996mg), potassium carbonate (828mg) and 1-bromo-3-fluoro-propane (846mg) in dry acetonitrile (2ml) for 30 minutes at 20°C and then at 60°C for 2 hours. Water (10 ml) is added and the mixture is extracted with ethyl acetate (30ml). The extract is washed with water (2x20ml), dried (MgSO_4) and evaporated to dryness. Purification by flash chromatography on a column of silicagel eluted with hexane:ethyl acetate (3:2, by vol.) affords the product, 1-benzyl-4-(3-fluoro-propyl)-piperazine, as an oil.

b) 1-Benzyl-4-(3-fluoro-propyl)-piperazine (1.17g) is dissolved in a mixture of ethanol (34ml) and aqueous hydrochloric acid (M, 5.44ml) and hydrogenated for 2 hours at 20°C at atmospheric pressure in the presence of 10% palladium on charcoal (165mg). The catalyst is removed by filtration and the solvent evaporated to give 1-(3-fluoro-propyl)-piperazine hydrochloride as a solid which is stored in vacuo (P_2O_5).

INTERMEDIATE 2-10

a) 1-Benzyl-4-(2,2-difluoro-ethyl)-piperazine is prepared as described for Intermediate 2-9a but starting from 2-bromo-1,1-difluoro-ethane and stirring for 30 minutes at 20°C and then 18 hours at 60°C and worked up as described above.

b) 1-Benzyl-4-(2,2-difluoro-ethyl)-piperazine is hydrogenated as described for Intermediate 2-9b to give 1-(2,2-difluoro-ethyl)-piperazine hydrochloride as an oil.

INTERMEDIATE 2-11

a) 1-Benzyl-piperazine (3.7g), 4-bromo-butyric acid ethyl ester (3.9g) and tri-ethylamine (2.93ml) are stirred at 20°C for 16 hours. The reaction mixture is partitioned between water (200ml) and chloroform (200ml). The organic extract is dried (MgSO₄) and evaporated to give a yellow oil (6.10g) which is purified by elution from a pad of silicagel with ethyl acetate to give pure 4-(4-benzyl-piperazin-1-yl)-butyric acid ethyl ester as a colourless oil.

b) 4-(4-Benzyl-piperazin-1-yl)-butyric acid ethyl ester (4.7g) is dissolved in ethanol (160ml), aqueous hydrochloric acid (M, 17.6ml) is added and the mixture is hydrogenated (1 bar) in the presence of 10% palladium on charcoal (0.47g) at 20 °C until the reaction is complete. The catalyst is removed by filtration and the filtrate evaporated to give 4-piperazin-1-yl-butyric acid ethyl ester hydrochloride as a gum containing residual solvent which is kept in vacuo (NaOH pellets).

The following compounds are prepared by the methods described above for Intermediate 2-11:

INTERMEDIATE 2-12

a) 5-(4-Benzyl-piperazin-1-yl)-pentanoic acid ethyl ester (after flash chromatography) as an oil.

b) 5-Piperazin-1-yl-pentanoic acid ethyl ester hydrochloride as an oil which crystallises on storage.

INTERMEDIATE 2-13

- a) 6-(4-Benzyl-piperazin-1-yl)-hexanoic acid ethyl ester as an oil.
- b) 6-Piperazin-1-yl hexanoic acid ethyl ester hydrochloride as an oil which crystallises on storage.

INTERMEDIATE 2-14

- a) 7-(4-Benzyl-piperazin-1-yl)-heptanoic acid ethyl ester as an oil.
- b) 7-Piperazin-1-yl-heptanoic acid ethyl ester hydrochloride as an oil which crystallises on storage.

INTERMEDIATE 2-15

- a) 3-Chlorocarbonyl propionic acid benzyl ester (4.53g) is dissolved in dichloromethane (30ml) and the solution is cooled to -20°C. 4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (4.58g) is added followed by triethylamine (2.79ml) to pH9. The reaction mixture is stirred at 20° for 16 hours. The solvent is removed by evaporation and the crude residue of succinic acid benzyl ester 2-(1-tert.-butoxycarbonyl-piperidin-4-yl)-ethyl ester is kept in vacuo (NaOH pellets).
- b) From succinic acid benzyl ester 2-(1-tert.-butoxycarbonyl-piperidin-4-yl)-ethyl ester using the procedure described for Intermediate 2-5b there is obtained succinic acid benzyl ester 2-piperidin-4-yl-ethyl ester hydrochloride which is kept in vacuo (NaOH pellets).

INTERMEDIATE 2-16

Piperidin-4-yl-ethanol (1.5g) is dissolved in dichloromethane (30ml) and cooled with stirring to 0-5°C. Trifluoromethane sulphonic acid (2.86g) is added dropwise at <5°C and iso-butylene is passed through the solution for 1 hour at <5°C. The mixture is stirred for 1 hour at 20°C and aqueous potassium carbonate (50%, 20ml) added dropwise over 10 minutes with stirring followed by ether (20ml). The aqueous phase is extracted with further portions (3x50ml) of ether, the combined extracts are dried (MgSO₄) and the solvent evaporated to give a light yellow oil which is distilled (50°C/0.4mm) to yield pure 4-(2-tert.-butoxy-ethyl)-piperidine.

INTERMEDIATE 2-17

a) 3-Mercapto-propionic acid ethyl ester (0.65ml) is added to sodium methoxide solution (from 115.5mg of sodium dissolved in 5ml dry methanol) and 4-(2-bromo-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (1.46g) is added. The mixture is heated at reflux for 2 hours, cooled and water (5ml) is added. The solution is extracted with ether (2x20ml), the combined extracts dried (MgSO₄) and the ether evaporated under reduced pressure.

The residue is purified by chromatography on a column of silicagel (230-400 mesh) which is eluted with chloroform. By combination of appropriate fractions and evaporation of the solvent, pure 4-[2-(2-ethoxycarbonyl-ethylsulfanyl)-ethyl]-piperidine-1-carboxylic acid tert.-butyl ester is obtained as an oil.

b) 4-[2-(2-Ethoxycarbonyl-ethylsulfanyl)-ethyl]-piperidine-1-carboxylic acid tert.-butyl ester (1.4g) is dissolved in saturated hydrogen chloride in acetic acid (12ml) and the solution is stirred for 2 hours at 20°C. The solvent is removed by evaporation at reduced pressure and portions of methanol (2x50ml) are evaporated from the residue to give 4-(2-piperidin-4-yl-ethylsulfanyl)-propionic acid ethyl ester hydrochloride which is held in vacuo (NaOH pellets).

INTERMEDIATE 2-18

a) Analogously as described for Intermediate 2-17a but using dihydrothiophen-2-one and 4-(2-bromo-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester and reaction conditions of 16 hours at 20°C is prepared 4-[2-(3-carboxy-propylsulfanyl)-ethyl]-piperidine-1-carboxylic acid tert.-butyl ester as an oil.

b) 4-[2-(3-Carboxy-propylsulfanyl)-ethyl]-piperidine-1-carboxylic acid tert.-butyl ester (1.41g) is dissolved in ethanol (50ml) and hydrogen chloride gas is bubbled slowly through the solution for 3 hours. The solvent is evaporated and the residue of 4-(2-piperidin-4-yl-ethylsulfanyl)-butyric acid ethyl ester hydrochloride is kept in vacuo (NaOH pellets).

INTERMEDIATE 2-19

a) 4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (7.15g) is dissolved in dry pyridine (100ml) and 2,2-dimethyl-propionyl chloride (9.64g) is added at 0°C. The mixture is stirred for 16 hours and the solvent removed by rotary evaporation. Portions (3x50ml) of ethanol are evaporated from the residue which is partitioned between ethyl acetate and water (100ml of each). The organic layer is dried (MgSO₄) and evaporated to give 4-[2-(2,2-dimethyl-propionyloxy)-ethyl]-piperidine-1-carboxylic acid tert.-butyl ester as an oil.

b) Treatment of 4-[2-(2,2-dimethyl-propionyloxy)-ethyl]-piperidine-1-carboxylic acid tert.-butyl ester with hydrogen chloride in acetic acid as described for Intermediate 2-5b gives 2,2-dimethyl-propionic acid 2-piperidin-4-yl-ethyl ester.

INTERMEDIATE 2-20

a) Formaldehyde solution (21.9ml) is added to a stirred solution of 1-benzyl-piperazine (15ml) and diethyl phosphite (36ml) in dioxan (10ml) at 20°C. The temperature of the mixture rises to 50°C. The mixture is stirred for 30 minutes. Solvent and excess of reagent are removed by distillation and the crude product is purified by flash chromatography on a column of silicagel using chloroform:methanol (9:1, by vol.) as eluant to afford pure (1-benzyl-piperazin-4-ylmethyl)-phosphonic acid diethyl ester.

b) (1-Benzyl-piperazin-4-ylmethyl)-phosphonic acid diethyl ester (980mg) is dissolved in dry methanol (20ml), 10% palladium on charcoal (980mg) and ammonium formate (945mg) are added and the mixture is heated at reflux until reaction is complete. The catalyst is removed by filtration and the solvents evaporated to give crude material which is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (7:13, by vol.) to give piperazin-4-ylmethyl-phosphonic acid diethyl ester which is stored in vacuo.

INTERMEDIATE 2-21

a) 6-Pyridin-4-yl-hexan-1-ol (4.65g) is dissolved in ethanol (120ml), conc. aqueous hydrochloric acid (2.5ml) is added and the mixture is hydrogenated in the presence of Adam's catalyst (1g) at 20°C for 16 hours. The catalyst is removed by filtration through a pad of Celite and solvents removed by rotary evaporation to give 6-piperidin-4-yl-hexan-1-ol hydrochloride as a light orange solid which is stored in vacuo (NaOH pellets).

b) 6-Piperidin-4-yl-hexan-1-ol hydrochloride (5.5g) is heated to 120°C (oil-bath) to melt the substance. Phosphorus tribromide (1.43g) is added dropwise over several minutes with stirring and the mixture is then cooled to give crude 4-(6-bromo-hexyl)-piperidine hydrobromide salt as a viscous oil which is stored in vacuo (NaOH pellets). The residue is dissolved in 50% aqueous dioxan (100ml) and adjusted to pH 7 by the addition of solid sodium bicarbonate. By a standard method, using di-t.-butoxy carbonate is prepared 4-(6-bromo-hexyl)-piperidine-1-carboxylic acid tert.-butyl ester as a pale orange oil.

c) 4-(6-Bromo-hexyl)-piperidine-1-carboxylic acid tert.-butyl ester (7.16g) and triethyl phosphite (30ml) are heated at 160-165°C for 7 hours and the mixture is then stirred at 20°C for 16 hours. Excess of reagent is removed by vacuum distillation and the residue is purified by chromatography on a column of silicagel using ethyl acetate:hexane (7:3, by vol.) as eluant to afford 4-[6-(diethoxy-phosphoryl)-hexyl]-piperidine-1-carboxylic acid tert.-butyl ester as an oil which is stored in vacuo (NaOH pellets).

d) 4-[6-(Diethoxy-phosphoryl)-hexyl]-piperidine-1-carboxylic acid tert.-butyl ester (1.6g) is converted to (6-piperidin-4-yl-hexyl)-phosphonic acid diethyl ester hydrochloride as described for Intermediate 2-5b.

INTERMEDIATE 2-22

a) (2-Chlorocarbonyl-ethyl)-phosphonic acid diethyl ester (6.66g) is dissolved in DMF (30ml) and cooled to -15°C, NMM (3.48ml) is added followed by isobutyl chloroformate (4.14ml). The mixture is stirred at -15°C for 15 minutes. A solution of 4-(2-amino-ethyl)-pyridine (3.93g) in DMF (5ml) at -15°C is added to this solution, the pH adjusted to 8 (NMM) and the mixture stirred at -15°C for 30 minutes and then at 20°C for 16 hours. Solvents are removed by rotary evaporation and the residue is dissolved in chloroform (100ml) and washed with water (3x100ml), dried and evaporated to afford [2-(2-pyridin-4-yl-ethylcarbamoyl)-ethyl]-phosphonic acid diethyl ester as an oil, stored in vacuo (NaOH pellets).

b) [2-(2-Pyridin-4-yl-ethylcarbamoyl)-ethyl]-phosphonic acid diethyl ester (11.83g) is dissolved in methanol:acetic acid (9:1, by vol., 30ml) and hydrogenated (1 bar) at 20°C for 16 hours in the presence of 10% palladium on charcoal (500mg). The catalyst is removed by filtration and the filtrate dried by rotary evaporation to give [2-(2-pyridin-4-yl-ethylcarbamoyl)-ethyl]-phosphonic acid diethyl ester as an oil which is stored in vacuo (NaOH pellets).

INTERMEDIATE 2-23

a) Analogously as described for Intermediate 2-8a but using 4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazine in place of 2-piperazin-1-yl-ethanol is prepared 4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazine-1-carboxylic acid tert.-butyl ester.

b) 4-[2-(2-Hydroxy-ethoxy)-ethyl]-piperazine-1-carboxylic acid tert.-butyl ester (548mg) is dissolved in dry THF (5ml) and sodium hydride dispersion (60%, 80mg) is added. The mixture is stirred at 20°C for 1 hour and acetyl chloride (0.135ml) is added slowly. The mixture is stirred overnight, solvents are removed by rotary evaporation and the residue is dissolved in ethyl acetate (10ml). The solution is washed with portions (2x20ml) of water and brine (20ml), dried (MgSO₄) and solvent evaporated to give crude material which is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:1, by vol.) as eluant to give 4-[2-(2-acetoxy-ethoxy)-ethyl]-piperazine-1-carboxylic acid tert.-butyl ester as a yellow oil.

c) 4-[2-(2-Acetoxy-ethoxy)-ethyl]-piperazine-1-carboxylic acid tert.-butyl ester (220mg) is dissolved in dichloromethane (3ml) and trifluoroacetic acid (0.40ml) is added. The mixture is stirred at 20°C for 16 hours, evaporated to dryness and the residue of acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester trifluoroacetate salt is held in vacuo (NaOH pellets). It is suitable for direct use.

INTERMEDIATE 2-24

a) 4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (18.7g) is dissolved in dry dichloromethane (50ml) and carbon tetrabromide (40.7g) is added. Triphenyl phosphine (21.4g) is added in dry dichloromethane (50ml) slowly over 2 hours. The mixture is stirred at 20°C for 2 hours, hexane (500ml) is added to the mixture which is washed with portions (2x100ml) of saturated aqueous sodium bicarbonate, water, brine, dried (MgSO₄) and the solvents evaporated to give an oil which is purified using a pad of silicagel which is eluted with ether:hexane (1:9 followed by 3:7, by vol.) to afford 4-(2-bromo-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester as an oil which slowly crystallises on storage (m.p. 39-42°C).

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b) 1,4-Butanediol (3.52ml) and sodium (0.46g) are heated at 125°C in xylene (10ml) to give a solution to which 4-(2-bromo-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (5.84g) is added. The mixture is heated at 125°C for 16 hours, the solvent evaporated and the residue partitioned between chloroform and water. Evaporation of the organic phase gives crude material which is purified by flash chromatography on a column of silicagel using ethyl acetate as eluant to give 4-[2-(4-hydroxy-butoxy)-ethyl]-piperidine-1-carboxylic acid tert.-butyl ester.

c) A solution of 4-[2-(4-hydroxy-butoxy)-ethyl]-piperidine-1-carboxylic acid tert.-butyl ester (1.44g) is added in DMF (10ml) to a solution of pyridinium dichromate (6.3g) in DMF (20ml) and stirred for 16 hours at 20°C. The mixture is poured into water (400ml) which is extracted with ether (3x50ml), the combined extracts are dried (Na₂SO₄) and the solvent evaporated to give 4-[2-(3-carboxy-propoxy)-ethyl]-piperidine-1-carboxylic acid tert.-butyl ester.

d) 4-[2-(3-Carboxy-propoxy)-ethyl]-piperidine-1-carboxylic acid tert.-butyl ester is converted to 4-(2-piperidin-4-yl-ethoxy)-butyric acid ethyl ester hydrochloride as described for Intermediate 2-18b and the product is kept in vacuo (NaOH pellets).

INTERMEDIATE 2-25

a) Thionyl chloride (1.03ml) is added to 6-pyridin-4-yl-hexan-1-ol hydrochloride (2.42g) and the mixture is stirred at 20°C for 30 minutes. Excess of saturated aqueous sodium bicarbonate and chloroform (20ml) are added. The organic phase is washed with saturated aqueous sodium bicarbonate, brine and water, dried (MgSO₄) and the solvent evaporated to give crude material which is purified by flash chromatography on a column of silicagel (methanol:chloroform = 1:49, by vol.) to give 4-(6-chloro-hexyl)-pyridine as an oil.

b) Sodium cyanide (509mg) in dimethyl sulfoxide (4.25ml) is added to 4-(6-chloro-hexyl)-pyridine (1.71g) dissolved in dimethylsulfoxide (4.25ml). The mixture is stirred at 60°C for 3 hours, poured into water (100ml) and extracted with chloroform (3x15ml). The combined extracts are washed with water (2x20ml), dried (Na₂SO₄) and the solvent evaporated to give 7-pyridin-4-yl-heptanenitrile.

c) 7-Pyridin-4-yl-heptanenitrile (1.45g) is stirred at 60-70°C for 72 hours with a mixture of ethanol (3.6ml) and concentrated aqueous hydrochloric acid (3.6ml). The cooled reaction mixture is partitioned between water (20ml) and chloroform (20ml) and the separated organic phase dried (Na_2SO_4) and evaporated to yield crystalline 7-pyridin-4-yl-heptanoic acid ethyl ester hydrochloride.

d) 7-Pyridin-4-yl-heptanoic acid ethyl ester hydrochloride (1.17g) is dissolved in methanol (22.5ml) and acetic acid (2.5ml) and hydrogenated (1 bar) in the presence of Adam's catalyst (100mg) at 20°C for 16 hours. The catalyst is removed by filtration and the solvents evaporated to give 7-piperidin-4-yl-heptanoic acid ethyl ester hydrochloride which is kept in vacuo (NaOH pellets).

INTERMEDIATE 2-26

a) Piperidin-4-one monohydrate hydrochloride (23.0g) is dissolved in water (75ml) and the solution is stirred and cooled to between 0°C and 5°C and triethylamine (66ml) is added. To the stirred mixture at 0°C to 5°C is added slowly a solution of di-tert.-butyl dicarbonate (44.5g) in THF (75ml) and stirring is continued at room temperature for 4 hours. The mixture is concentrated by evaporation to give a white suspension, from which solid is collected by filtration, washed with water and dried. Recrystallisation from hexane give 4-oxo-piperidine-1-carboxylic acid tert.-butyl ester as white needles, m.p. 72.4°C.

b) Sodium hydride (0.66g) is suspended in dry toluene (50ml) and tetraethylmethylenediphosphonate (7.93g) dissolved in dry toluene (30ml) is added slowly with stirring keeping the temperature below 25°C. After 10 minutes, when a clear solution has formed, a solution of 4-oxo-piperidine-1-carboxylic acid tert.-butyl ester (4.98g) in dry toluene (30ml) is added slowly with stirring below 25°C and stirring is continued at room temperature for 2 hours. Water (50ml) is added and the toluene layer is separated, washed with water (2x50ml) and dried (MgSO_4). The toluene is evaporated to give an oil, which is purified by chromatography on a column of silicagel using ethyl acetate as eluant to yield 4-(diethoxy-phosphorylmethylene)-piperidine-1-carboxylic acid tert.-butyl ester, having ^{31}P - and ^{13}C -NMR spectra consistent with the claimed structure.

c) 4-(Diethoxy-phosphorylmethylene)-piperidine-1-carboxylic acid tert.-butyl ester (18g) is dissolved in methanol (350ml) and hydrogenated (1 bar) in the presence of 5% palladium on charcoal (1g) for 20 hours at 30°C. Removal of the catalyst and solvent gives 4-(diethoxy-phosphorylmethyl)-piperidine-1-carboxylic acid tert.-butyl ester as a colourless oil, having ³¹P- and ¹³C-NMR spectra consistent with the claimed structure.

d) To a stirred solution of 4-(diethoxy-phosphorylmethyl)-piperidine-1-carboxylic acid tert.-butyl ester (0.5g) in dichloromethane (3ml) cooled to 0-5°C is slowly added trifluoroacetic acid (3ml) and the reaction mixture is allowed to stay at room temperature for 50 minutes. Toluene (3ml) is added and the mixture is concentrated by evaporation and co-evaporated with further portions (2x3ml) of toluene to give diethyl piperidin-4-yl methane phosphonate trifluoroacetate salt as an oil. This is dissolved in aqueous 50% potassium carbonate (2.5ml), which is extracted with ethyl acetate (4x10ml). The combined extracts are dried (MgSO₄) and evaporated to a white foam, which is the free base piperidin-4-ylmethyl-phosphonic acid diethyl ester, having ³¹P- and ¹³C-NMR spectra consistent with the claimed structure.

INTERMEDIATE 2-27

a) 4-(2-Oxo-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (1.77g) and trifluoromethyl trimethyl silane (1.27g) are dissolved in THF (50ml) and TBAF (0.16ml) is added at 0°C under an atmosphere of nitrogen. The mixture is allowed to warm to room temperature and, after keeping for 2 hours, 10% aqueous citric acid (20ml) is added and the mixture is extracted with ethyl acetate (30ml). The extract is washed with brine (30ml), dried (MgSO₄) and the solvent evaporated to give 4-(2,2,2-trifluoro-1(RS)-hydroxy-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester as a colourless oil.

b) 4-(2,2,2-Trifluoro-1(RS)-hydroxy-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (1.25g) is treated as described for Intermediate 2-5b to give 2,2,2-trifluoro-1(RS)-piperidin-4-yl-ethanol hydrochloride as a white solid which is held in vacuo (NaOH pellets).

INTERMEDIATE 2-28

Piperidin-2(S)-ylmethanol (6.45g) in dichloromethane (140ml) is cooled to 0-5°C and concentrated sulphuric acid (5.5g) is added dropwise with vigorous stirring. Isobutylene is bubbled through the mixture for 1 hour with the temperature maintained at 0-5°C. Concentrated sulphuric acid (1.37g) is added dropwise. The mixture is closed securely and allowed to warm to room temperature with vigorous stirring for five hours. The mixture is cooled to 0-5°C and aqueous potassium carbonate (50% w/v, 85ml) is added slowly, followed by diethyl ether (85ml). The organic layer is separated and the aqueous phase is washed with diethyl ether (2x75ml). The combined organic layers are washed with brine (2x50 ml), dried (MgSO₄), filtered and evaporated to give an oil which is distilled. The fraction boiling at 66-7°C at 3.5 mm is collected to give 2(S)-tert.-butoxymethyl-piperidine, $[\alpha]_D^{26} + 20.5^\circ$ (c = 2, ethanol).

INTERMEDIATE 2-29

Analogously as described for Intermediate 2-28 but using piperidin-2(R)-ylmethanol in place of piperidin-2(S)-ylmethanol is prepared 2(R)-tert.-butoxymethyl-piperidine.

INTERMEDIATE 2-30

Analogously as described for Intermediate 2-28 but using 2-piperidin-2(RS)-yl-ethanol in place of piperidin-2(S)-ylmethanol is obtained 2(RS)-(2-tert.-butoxy-ethyl)-piperidine as an oil, b.p. 68-9°C/2.0 mm.

INTERMEDIATE 2-31

Analogously as described for Intermediate 2-28 but using piperidin-3(RS)-ol in place of piperidin-2(S)-ylmethanol is prepared 3(RS)-tert.-butoxy-piperidine as an oil, b.p. 80-90°C/0.3mm.

INTERMEDIATE 2-32

Pyridin-4-yl-acetamide (5g) is dissolved in glacial acetic acid (70 ml) and hydrogenated (1 bar) in the presence of platinum oxide (200mg) for 48 hours at 30°C. Removal of catalyst and solvent gives the acetate salt which is dissolved in water (75ml) and basified by addition of aqueous sodium carbonate (2M). Evaporation of the mixture gives a residue which is leached with several portions (25ml) of 4-methyl-2-pentanone. The combined extracts are evaporated to yield 4-carbamoylmethyl-piperidine.

INTERMEDIATE 2-33

Analogously as described for Intermediate 2-28 but using 3-piperidin-4-yl-propan-1-ol hydrochloride in place of piperidin-2(S)-ylmethanol is prepared 4-(3-tert.-butoxy-propyl)-piperidine as an oil.

INTERMEDIATE 2-34

Analogously as described for Intermediate 2-28 but using 3-piperidin-3(RS)-yl-propan-1-ol hydrochloride in place of piperidin-2(S)-ylmethanol is prepared 3(RS)-(3-tert.-butoxy-propyl)-piperidine as an oil.

INTERMEDIATE 2-35

Analogously as described for Intermediate 2-28 but using piperidin-4-ol in place of piperidin-2(S)-ylmethanol is prepared 4-tert.-butoxy-piperidine as an oil, b.p. 50-60°C/0.44mm.

INTERMEDIATE 2-36

Analogously as described for Intermediate 2-28 but using piperidin-4-ylmethanol in place of piperidin-2(S)-ylmethanol is prepared 4-tert.-butoxymethyl-piperidine as an oil, b.p. 70-80°C/0.6mm.

INTERMEDIATE 2-37

Analogously as described for Intermediate 2-28 but using piperidin-(3R)-ylmethanol in place of piperidin-2(S)-ylmethanol is prepared 3(R)-tert.-butoxymethyl-piperidine as an oil, b.p. 90°C/1.5mm.

INTERMEDIATE 2-38

a) 3-Chlorocarbonyl propionic acid methyl ester (6.8ml) is dissolved in dichloromethane (65ml) at -20°C with exclusion of moisture (CaCl₂ tube). 2-Pyridin-4-yl-ethylamine (5.04g) and triethylamine (6.2ml) are added in two equal portions to the solution and the mixture is stirred at 20°C for 16 hours. The mixture is filtered and the filtrate evaporated to dryness. Flash chromatography of the residue on a column of silicagel using ethyl acetate as eluant gives N-(2-pyridin-4-yl-ethyl)-succinamic acid methyl ester as a light orange solid.

b) N-(2-Pyridin-4-yl-ethyl)-succinamic acid methyl ester (7.5g) is dissolved in ethanol (100ml) and aqueous hydrochloric acid (4M, 1 equiv.) is added. The mixture is hydrogenated in the presence of Adam's catalyst (1.2g) for 16 hours at 20°C and the catalyst removed by filtration through a pad of Celite. Evaporation of the filtrate gives N-(2-piperidin-4-yl-ethyl)-succinamic acid methyl ester hydrochloride as a colourless oil which is kept in vacuo (NaOH pellets).

INTERMEDIATE 2-39

Analogously as described for Intermediate 2-28 but using 2-piperidin-3(R)yl-ethanol in place of piperidin-2(S)-ylmethanol is prepared 3(R)-(2-tert.-butoxy-ethyl)-piperidine as an oil.

INTERMEDIATE 2-40

- a) Piperazine-1-carboxylic acid tert.-butyl ester (559mg) is dissolved in isopropanol (5ml) and 2(RS)-fluoromethyl-oxirane (0.214ml) is added. The solution is stirred at 20°C for 4 hours, evaporated and the residue purified by flash chromatography on a column of silicagel using dichloromethane:methanol (49:1, by vol.) as eluant to give 4-(3-fluoro-2(RS)-hydroxy-propyl)-piperazine-1-carboxylic acid tert.-butyl ester as a colourless oil.
- b) 4-(3-Fluoro-2(RS)-hydroxy-propyl)-piperazine-1-carboxylic acid tert.-butyl ester (570mg) is converted as described for Intermediate 2-23c to 1-fluoro-3-piperazin-1-yl-propan-2(RS)-ol trifluoroacetic acid salt as a yellow oil which is kept in vacuo (NaOH pellets).

EXAMPLE 1

- a) (S)-Arginine (12.6g) and potassium carbonate (12.03g) are suspended in 50% water/dioxan (250ml) with vigorous stirring and the reaction mixture is cooled to <5°C. 3-(1-Methyl-1-phenyl-ethyl)-benzenesulfonyl chloride (21.4g) is added in 6 portions over 30 minutes at <5°C. The mixture is stirred at 20°C for 2 hours. A colourless solid precipitates. The dioxan is removed by evaporation and the aqueous residue is acidified with conc. aqueous hydrochloric acid. The mixture is extracted with ethyl acetate (3x50ml) and the aqueous phase and all solid materials are combined and neutralised with aqueous sodium hydroxide (4M). The suspension is stirred for 16 hours at 20°C. The solid precipitate is collected by filtration and stirred for 16 hours with a little water. The solid is collected by filtration and dried (NaOH pellets) to give 5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoic acid, m.p. 122-124°C. (Found: C, 53.49; H, 6.81; N, 11.92; S, 6.93. $C_{21}H_{28}N_4O_4S \cdot 2.3H_2O$ requires C, 53.22; H, 6.93; N, 11.82; S, 6.77%).

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b) 5-Guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoic acid (936mg) is stirred with thionyl chloride (5ml) for 2 hours at 20°C. Dry ether (40ml) is added with vigorous stirring. The supernatant liquid is decanted from the white gum formed which is triturated with portions (2 x 40ml) of dry ether. The gum is kept in vacuo (NaOH pellets) for 20 minutes to give a crisp white foam of 5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl chloride hydrochloride salt.

c) Pyrrolidin-2(R)-ylmethanol (204mg) and triethylamine (0.28ml) are dissolved in DMF (5ml) and cooled in ice. 5-Guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl chloride hydrochloride salt (953mg) dissolved in DMF (2ml) is added dropwise during 10 minutes with stirring below 5°C (pH >9). After stirring for a further 30 minutes, the mixture is filtered and the filtrate is evaporated to dryness and the residual oil is freed of DMF by co-evaporation of the residue with ethanol (2x5ml). The resultant oil is dissolved in methanol (2ml) and added dropwise to vigorously stirred Na-dried ether (25ml). The supernatant liquid is decanted and the residual gum held in vacuo (conc. sulphuric acid) to give a crisp foam (1.09g). The product is isolated from the foam by preparative high pressure liquid chromatography (HPLC) (Zorbax C8) using acetonitrile:water:acetic acid (330:670:1, by vol.) to give 100mg of crude product which is purified by dissolution in a mixture of acetic acid (M, 3ml) and aqueous hydrochloric acid (M, 2ml) and passage through a column (40x3cm) of Biogel-P2 resin which is eluted with aqueous acetic acid (M) to give the hydrochloride salt of N-[4-guanidino-1(S)-(2(R)-hydroxymethyl-pyrrolidine-1-carbonyl)-butyl]-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide as lyophilised material, m.p. 103-106°C. (Found: C, 54.82; H, 7.00; N, 12.30; S, 5.73; Cl, 6.60. C₂₆H₃₇N₅O₄S.HCl.H₂O requires C, 54.77; H, 7.07; N, 12.28; S, 5.62; Cl, 6.22%).

EXAMPLE 2

a) (S)-Arginine (2.56g) and potassium carbonate are dissolved in water (25ml) at 0°C and 3-methylquinolinyl-8-sulfonyl chloride (3.55g) dissolved in benzene (25ml) and dichloromethane (25ml) is added during 30 minutes. The mixture is stirred for 5 hours and then stored at 0°C for 16 hours.

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The precipitated product is collected by filtration, washed with chloroform and water and dried in vacuo (KOH pellets), to give 5-guanidino-2(S)-(3-methylquinoline-8-sulfonyl-amino)-pentanoic acid. (Found: C, 47.21; H, 5.71; N, 17.18; S, 7.77. $C_{16}H_{21}N_5O_4S \cdot 1.4H_2O$ requires C, 47.27; H, 5.95; N, 17.23; S, 7.88%).

b) In a similar manner to that described for Example 1b-c but using 2-piperazin-1-yl-ethanol in place of pyrrolidin-2(R)-ylmethanol and 5-guanidino-2(S)-(3-methylquinoline-8-sulfonyl-amino)-pentanoyl chloride hydrochloride salt in place of 5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl chloride hydrochloride salt is prepared, after gel filtration chromatography on a column (90x3cm) of Biogel P2 resin using acetic acid (M) as eluant, 3-methylquinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-butyl}-amide hydrochloride salt.

c) The product of Example 2b is hydrogenated (1 bar, 10% palladium on charcoal, 20°C, 26 hours) in methanol:acetic acid; water (30:3:1, by vol.) at 68mM concentration. The product is isolated by preparative HPLC (using Zorbax C8 support) using acetonitrile:water:trifluoroacetic acid (200:800:1 by vol.) and converted to the acetate salt by filtration through Dowex 1 (acetate form) resin, to yield 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-butyl}-amide acetate, m.p. 62-65°C. (Found: C, 48.99; H, 7.41; N, 16.43; S, 5.38. $C_{22}H_{37}N_7O_4S \cdot CH_3COOH \cdot 2H_2O$ requires C, 48.71; H, 7.67; N, 16.57; S, 5.42%).

EXAMPLE 3

a) 5-(3-Nitro-guanidino)-2(S)-tert.-butoxycarbonylamino-pentanoic acid (31.9g) is dissolved in DMF (465ml) and NMM (31.9ml) is added. The mixture is cooled to -15°C and isobutyl chloroformate (38ml) is added. The reaction is stirred at -15°C for 15 minutes. Acetic acid 2-piperidin-4-yl ethyl ester hydrochloride (60g) is dissolved in DMF (465ml) with NMM (31.9ml) and the solution is cooled to -15°C. The two solutions are combined with stirring below -10°C and stirring is continued for 30 minutes at -10°C and then at 20°C for 2 hours.

The solvent is removed by evaporation and the residue is dissolved in ethyl acetate (300ml) and the solution washed with portions (2x250ml) of saturated aqueous sodium bicarbonate, brine, 7% aqueous citric acid and brine, dried (Na_2SO_4) and the solvent evaporated to yield 5-(3-nitro-guanidino)-2(S)-tert.-butoxycarbonylamino-1-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-pentan-1-one as a gum.

b) 5-(3-Nitro-guanidino)-2(S)-tert.-butoxycarbonylamino-1-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-pentan-1-one (127.6g) is dissolved in saturated hydrogen chloride in acetic acid (625ml) and the reaction mixture is stirred at 20°C for 2.5 hours. Evaporation of the solvent gives a chromatographically-pure residue of 2(S)-amino-5-(3-nitro-guanidino)-1-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-pentan-1-one hydrochloride which is kept in vacuo (NaOH pellets) for direct use in the following step.

c) The above 2(S)-amino-5-(3-nitro-guanidino)-1-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-pentan-1-one hydrochloride (128g) is suspended in dry DMF (1l) and Huenig Base (66.6ml) is added to give a solution at pH 9 which is cooled to between 0°C and 5°C (ice/salt). A further 46.6ml of Huenig Base is added followed by 3-methylquinoliny-8-sulfonyl chloride (65.4g) in 5 equal portions over 30 minutes and the reaction mixture is stirred at 20°C for 3 hours. The solvent is removed by evaporation and the residue is dissolved in dichloromethane (800ml) and the solution washed with portions (2x800ml) of 7% aqueous citric acid and water, the aqueous phase being back-washed with dichloromethane. The combined organic extracts are dried (Na_2SO_4) and the solvent evaporated to give a residue which is triturated with ether to give 3-methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-[4-(2-acetoxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide as a solid which is dried in vacuo. This is sufficiently pure for use in the following step.

d) 3-Methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-[4-(2-acetoxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide (29.2g) is dissolved in methanol (200ml) at 0°C and aqueous sodium hydroxide (M, 101.2ml) is added. The mixture is stirred at 20°C for 1 hour and aqueous hydrochloric acid (M, 101.2ml) is added.

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The solvents are removed by evaporation and the residue is shaken with chloroform (100ml). Solids are removed by filtration and washed with chloroform (100ml) and the combined chloroform extracts are purified in two equal batches by passage through a pad (500g, 13cm diameter) of silicagel (70-230 mesh) which is washed with chloroform (3.5l) and methanol:chloroform (5:95, by vol.), collecting the eluate in fractions (250ml). From a typical separation, fractions 14-29 afford, after evaporation of the solvent, 3-methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide as product with chromatographic purity >99.5% (HPLC). Impure side-fractions are stock-piled for recovery of further product by rechromatography.

e) 3-Methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide (60g) is dissolved in a mixture of ethanol (1.05l) and acetic acid (226ml) and hydrogenated (1 bar) in the presence of 10% palladium on charcoal (12.5g) for 92 hours at 20°C. Removal of the catalyst and solvent gives the acetate salt which is dissolved in isopropanol (300ml) and converted to the phosphate salt by the slow addition of a calculated quantity of phosphoric acid (88%, sp. gr. 1.75) in isopropanol. Addition of ether (2l) to this solution with vigorous stirring gives a solid which is washed with ether and dried to constant weight. This is dissolved in water (84ml) and passed through a column (350ml) of Dowex 1 (chloride form) resin which is eluted with water (700ml). Water is removed by rotary evaporation and the residue is dried by addition and evaporation of ethanol (3x100ml). The residue is dissolved in methanol (50ml) and added to vigorously-stirred dry ether (1l) to give 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide hydrochloride as a stable solid m.p. 108-112°C. (Found: C, 51.26; H, 7.50; N, 15.41; S, 5.66; Cl, 6.52. C₂₃H₃₈N₆O₄S.HCl.4H₂O requires C, 51.15; H, 7.46; N, 15.56; S, 5.94; Cl, 6.56%).

EXAMPLE 4

a) Using a procedure similar to that described for Example 3a but using 4-(2-tert.-butoxy-ethyl)-piperidine in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 5-(3-nitro-guanidino)-2(S)-tert.-butoxycarbonylamino-1-[4-(2-tert.-butoxy-ethyl)-piperidin-1-yl]-pentan-1-one.

- b) Using a modified procedure similar to that described for Example 3b but using 5-(3-nitro-guanidino)-2(S)-tert.-butoxycarbonylamino-1-[4-(2-tert.-butoxy-ethyl)-piperidin-1-yl]-pentan-1-one in place of 5-(3-nitro-guanidino)-2(S)-tert.-butoxycarbonylamino-1-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-pentan-1-one is achieved selective deprotection (at 0.04M dilution) using 1 equivalent of hydrogen chloride in acetic acid:dichloromethane (1:2, by vol.) at 0°C for 45 minutes to obtain 2(S)-amino-5-(3-nitro-guanidino)-1-[4-(2-tert.-butoxy-ethyl)-piperidin-1-yl]-pentan-1-one hydrochloride.
- c) Using a procedure similar to that described for Example 3c but using 2(S)-amino-5-(3-nitro-guanidino)-1-[4-(2-tert.-butoxy-ethyl)-piperidin-1-yl]-pentan-1-one hydrochloride in place of 2(S)-amino-5-(3-nitro-guanidino)-1-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-pentan-1-one hydrochloride is prepared 3-methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-[4-(2-tert.-butoxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide.
- d) Using a procedure similar to that described for Example 3e but using 3-methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-[4-(2-tert.-butoxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide in place of 3-methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-[4-(2-acetoxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide, hydrogenation is carried out (10% palladium on charcoal, 1 bar) in methanol:water:acetic acid (150:10:1, by vol.) to give 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-tert.-butoxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide acetate.
- e) Treatment of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-tert.-butoxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide acetate with hydrogen chloride in acetic acid as described for Example 3b gives 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide hydrochloride identical with that obtained in Example 3e.

EXAMPLE 5

3-Chlorocarbonyl-3-methyl-butyric acid benzyl ester (3.5g) and 3-methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide (1.7g) are dissolved in pyridine (42ml) at 20°C and stirred for 72 hours. The solvent is removed by rotary evaporation and the product recovered by flash chromatography on a column of silicagel using chloroform:methanol:acetic acid (6:1:1, by vol.) as eluant to give impure material which is hydrogenated (0.5g, 10% palladium on charcoal, 1 bar, 24 hrs and 20°C) in methanol:acetic acid (40ml+2ml). The product is recovered by flash chromatography on a column of silicagel using chloroform:methanol:acetic acid (6:1:1, by vol.) as eluant and lyophilised to afford 2,2-dimethyl-succinic acid 1-(2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl) ester acetate salt. (Found: C, 51.9; H, 7.5; N, 10.0; S, 4.0. C₂₉H₄₆N₆O₇S.CH₃COOH.2H₂O requires C, 51.8; H, 7.6; N, 11.7; S, 4.5%).

EXAMPLE 6

- a) Using the procedures described for Example 3a-c but using NMM as base and 3-piperidin-4-yl-propionic acid methyl ester in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 3-{1-[5-(3-nitro-guanidino)-2(S)-(3-methylquinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-propionic acid methyl ester as a gum, isolated by flash chromatography.
- b) Using the procedure described for Example 3e without the subsequent conversion of the salt forms but using 3-{1-[5-(3-nitro-guanidino)-2(S)-(3-methylquinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-propionic acid methyl ester in place of 3-methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide is prepared 3-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-propionic acid methyl ester acetate salt as a white solid, m.p. 162-4°C. The ¹³C-NMR spectrum is consistent with the claimed structure.

c) Using the procedure described for Example 3d but using 3-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-propionic acid methyl ester acetate salt in place of 3-methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-[4-(2-acetoxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide is prepared 3-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-propionic acid isolated, after addition of the calculated amount of aqueous hydrochloric acid, as the di-hydrochloride in the form of a lyophilised stable solid, m.p. 215⁰C. (Found: C, 46.9; H, 7.0; N, 13.7; S, 5.4; Cl, 11.8. C₂₄H₃₈N₆O₅S.2HCl.H₂O requires C, 47.0; H, 6.9; N, 13.7; S, 5.2; Cl, 11.6%).

EXAMPLE 7

a) Using the procedures described for Example 6a-b but using 7-(piperidin-4-yl)-heptanoic acid ethyl ester hydrochloride and in place of 3-piperidin-4-yl-propionic acid methyl ester is prepared crude product which is purified by flash chromatography on a column of silicagel using butan-1-ol-acetic acid:water (10:1:3, by vol.) as eluant to give pure 7-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-heptanoic acid ethyl ester acetate salt.

b) Using the procedure described for Example 3d but using 7-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-heptanoic acid ethyl ester acetate salt in place of 3-methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-[4-(2-acetoxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide and omitting the final addition of hydrochloric acid is prepared, after lyophilisation from dilute acetic acid solution, 7-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-heptanoic acid di-acetate salt as a stable solid. (Found: C, 51.50; H, 7.54; N, 11.38; S, 4.31.

C₂₈H₄₆N₆O₅S.2CH₃COOH.2.5H₂O requires C, 51.67; H, 7.99; N, 11.30; S, 4.31%).

EXAMPLE 8

a) Analogously as described for Example 6a but using 3-(1-methyl-1-phenyl-ethyl)-benzene-sulfonyl chloride and piperidin-2(R)-yl carboxylic acid ethyl ester in place of 3-methylquinoline-8-sulfonyl chloride 3-piperidin-4-yl-propionic acid methyl ester is prepared [5-(3-nitro-guanidino)-2(S)-(3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino)-pentanoyl]-piperidin-2(R)-yl-carboxylic acid ethyl ester.

b) [5-(3-Nitro-guanidino)-2(S)-(3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino)-pentanoyl]-piperidin-2(R)-yl-carboxylic acid ethyl ester (2.1g) is dissolved in THF (40ml) and heated to reflux. A solution of lithium borohydride (2M) in tetrahydrofuran (3.4ml) is added dropwise and the solution heated at reflux for a further 45 minutes and then cooled to room temperature. The mixture is cooled to 5-10°C and water (15ml) is added dropwise. Solid potassium carbonate (5g) is added and the mixture stirred, allowing to come to room temperature over 30 minutes. The tetrahydrofuran is removed by evaporation and the aqueous residue is extracted with ethyl acetate (2x25 ml). The combined extracts are washed with aqueous potassium carbonate solution (10% by wt., 15ml) and saturated aqueous sodium chloride solution (15ml), dried (MgSO₄), filtered and evaporated to give a foam. After chromatography on a column of Kieselgel 40 using ethyl acetate:dichloromethane (3:7 then 1:1 then 7:3 by vol.) and finally acetone:ethyl acetate (1:1, by vol.) there is obtained N-[4-(3-nitro-guanidino)-1(S)-(2(R)-hydroxymethyl-piperidine-1-carbonyl)-butyl]-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide as a foam.

c) N-[4-(3-Nitro-guanidino)-1(S)-(2(R)-hydroxymethyl-piperidine-1-carbonyl)-butyl]-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide is treated as described for Example 6b but using methanol only as the solvent for hydrogenation to give N-[4-guanidino-1(S)-(2(R)-hydroxymethyl-piperidine-1-carbonyl)-butyl]-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide as a white solid after lyophilisation from aqueous solution. (Found: C, 56.56; H, 7.36; N, 12.15. C₂₇H₃₉N₅O₄S.2.5H₂O requires C, 56.42; H, 7.72; N, 12.19%).

EXAMPLE 9

Analogously as described for Example 4 but using 2(S)-tert.-butoxymethyl-piperidine in place of 4-(2-tert.-butoxy-ethyl)-piperidine and 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride is prepared the chloride salt of the product, N-[4-guanidino-1(S)-(2(S)-hydroxymethyl-piperidine-1-carbonyl)-butyl]-4-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide, which is suspended in chloroform and washed with ice-cold, aqueous 50% potassium carbonate. The chloroform phase is dried (MgSO₄) and evaporated to give as product the free base as a white foam after trituration with ether, filtration, washing with ether and drying in vacuo. (Found: C, 60.49; H, 7.32; N, 12.93. C₂₇H₃₉N₅O₄S.0.5H₂O requires C, 60.20; H, 7.48; N, 13.10%).

EXAMPLE 10

Analogously as described for Example 9 but using 2(R)-tert.-butoxymethyl-piperidine in place of 2(S)-tert.-butoxymethyl-piperidine and 3-methylquinoline-8-sulfonyl chloride in place of 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride and carrying out the hydrogenation step in methanol as described for Example 8c is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(2(R)-hydroxymethyl-piperidine-1-carbonyl)-butyl]-amide as a white solid. (Found: C, 50.56; H, 7.44; N, 16.10. C₂₂H₃₆N₆O₄S.2.5H₂O requires C, 50.26; H, 7.86; N, 15.99%).

EXAMPLE 11

Analogously as described for Example 10 but using 2(R)-tert.-butoxymethyl-pyrrolidine in place of 2(R)-tert.-butoxymethyl-piperidine is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(2(R)-hydroxymethyl-pyrrolidine-1-carbonyl)-butyl]-amide as a white solid. (Found: C, 49.81; H, 7.14; N, 16.65. C₂₁H₃₄N₆O₄S.2H₂O requires C, 50.18; H, 7.62; N, 16.72%).

EXAMPLE 12

a) Analogously as described for Example 4a but using 2(RS)-(2-tert.-butoxy-ethyl)-piperidine in place of 2(R)-tert.-butoxymethyl-pyrrolidine is prepared 5-(3-nitro-guanidino)-2(S)-tert.-butoxycarbonylamino-1-[2(RS)-(2-tert.-butoxy-ethyl)-piperidin-1-yl]-pentan-1-one as a mixture of diastereomers. Chromatography on a column of Kieselgel 40 using dichloromethane:ethyl acetate (1:1, by vol.) as eluant gives fractions containing essentially pure diastereomer A and pure diastereomer B as shown by a thin layer chromatography using ethyl acetate as solvent.

b) Analogously as described for the remainder of the steps in Example 9 using separately the two diastereomers described above in section (a) of this Example is prepared 3-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[2-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide (Isomer A) (Found: C, 48.72; H, 6.99; N, 14.78. $C_{23}H_{38}N_6O_4S \cdot 4H_2O$ requires C, 48.74; H, 8.18; N, 14.83%) and **EXAMPLE 13**, 3-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[2-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide (Isomer B) which has a ^{13}C -NMR spectrum consistent with the claimed structure.

EXAMPLE 14

Analogously as described for Example 6a-b but using 2(RS)-piperidine phosphonic acid dibenzyl ester in place of 3-piperidin-4-yl-propionic acid methyl ester and 2-naphthalene sulfonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride is prepared {1-[5-guanidino-2(S)-(naphthalene-2-sulfonylamino)-pentanoyl]-piperidin-2(RS)-yl}-phosphonic acid as a white solid. (Found: C, 47.04; H, 5.93; N, 13.08; S, 5.86 $C_{21}H_{30}N_5O_6PS \cdot 1.5H_2O$ requires C, 46.83; H, 6.18; N, 13.00%; S, 5.75).

EXAMPLE 15

Analogously as described for Example 1b-c but using (1,2,3,4-tetrahydro-isoquinolin-3(RS)-yl)-methanol and 5-guanidino-2(S)-naphthalenesulphonylamino-pentanoic acid is prepared naphthalene-2-sulfonic acid [4-guanidino-1(S)-(3(RS)-hydroxymethyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)-butyl]-amide hydrochloride salt isolated after purification by gel filtration chromatography as described for Example 1c and lyophilisation of the eluate. (Found: C, 55.35; H, 6.1; N, 12.4; S, 6.1; Cl 6.9. $C_{26}H_{31}N_5O_4S.HCl.H_2O$ requires: C, 55.4; H, 6.1; N, 12.4; S, 5.7; Cl, 6.3%).

The acetate salt is obtained after passage of an aqueous solution of the hydrochloride salt through a short column of Dowex-1 (acetate form) resin and lyophilisation of the eluate. (Found: C, 55.65; H, 5.9; N, 11.5; S, 5.4. $C_{26}H_{31}N_5O_4S.CH_3COOH.2H_2O$ requires C, 55.5; H, 6.5; N, 11.6; S, 5.3%).

EXAMPLE 16

Analogously as described for Example 10 but using 3(RS)-tert.-butoxy-piperidine in place of 2(R)-tert.-butoxymethyl-piperidine is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(3(RS)-hydroxy-piperidine-1-carbonyl)-butyl]-amide as a hygroscopic solid, m.p. $<50^{\circ}C$. MS(FAB) $[M+H]^+ = 467$. The ^{13}C -NMR spectrum is consistent with the claimed structure.

EXAMPLE 17

a) Analogously as described for Example 6a-b but using piperidin-4-ylmethanephosphonic acid diethyl ester in place of 3-piperidin-4-yl-propionic acid methyl ester and 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride is prepared (1-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperidin-4-ylmethyl)-phosphonic acid diethyl ester m.p. $144^{\circ}C$. The ^{13}C -NMR spectrum is consistent with the claimed product.

b) Ethylene is bubbled through dry dichloromethane (50ml) at 25°C for 10 minutes. Iodotrimethylsilane (3.2g) is added dropwise and, after stirring for 10 minutes, a solution of (1-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperidin-4-ylmethyl)-phosphonic acid diethyl ester (410mg) in dry dichloromethane (10ml) is added slowly. The reaction mixture is stoppered and stirred for 3 hours, after which time solvent is removed by evaporation and the residue is co-evaporated with ethanol (3 times) to give a residual orange oil. The oil is dissolved in aqueous ethanol (1:1, by vol., 35ml) and the solution is applied to a column (25ml) of Dowex 50 (H⁺ form) resin. The column is washed with 50% aqueous ethanol (140ml) to remove impurities and eluted with conc. ammonia:water:ethanol (1:4:5, by vol.). Appropriate fractions of the eluate are combined and evaporated and then co-evaporated (3 times) with ethanol to give (1-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperidin-4-ylmethyl)-phosphonic acid m.p. 188-192°C. (Found: C, 52.1; H, 6.9; N, 11.1. C₂₇H₄₀N₅O₆PS.1.5H₂O requires C, 52.25; H, 7.0; N, 11.3%).

EXAMPLE 18

Analogously as described for Example 10, except that a different final acidolysis procedure described below is employed, and using 3(R)-tert.-butoxymethyl-piperidine in place of 2(R)-tert.-butoxymethyl-piperidine is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(3(R)-tert.-butoxymethyl-piperidine-1-carbonyl)-butyl]-amide (798mg) as a white solid. This is dissolved in trifluoroacetic acid (20ml), stirred and cooled to -5°C and a stream of hydrogen bromide is introduced into the solution for 1 hour. The flask containing the mixture is stoppered and kept at 20°C for 2 hours. The mixture is concentrated under vacuum and the residue is triturated with ether to give an off-white solid which is co-evaporated (twice) with ether. The solid is dissolved in a mixture of water (10ml) and dioxan (5ml) and the solution is adjusted to pH>10 by addition of ammonia (sp. gr. .880) and extracted with ethyl acetate (3x20ml). The combined extracts are dried (MgSO₄) and evaporated and the residue obtained is triturated with ether to give a solid which is collected by filtration, washed with ether and dried in vacuo to give 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(3(R)-hydroxymethyl-piperidine-1-carbonyl)-butyl]-amide, m.p.60°C. The C-NMR spectrum is consistent with the claimed structure.

EXAMPLE 19

Analogously as described for Example 1b-c and 3b but using 5-guanidino-2(S)-naphthalenesulfonylamino-pentanoic acid and 2(R)-tert.-butoxymethyl-piperidine is prepared naphthalene-2-sulfonic acid [4-guanidino-1(S)-(2(R)-hydroxymethyl-pyrrolidine-1-carbonyl)-butyl]-amide isolated as the hydrochloride salt after purification by gel filtration chromatography as described for Example 1c and lyophilisation of the eluate. (Found: C, 49.91; H, 6.19; N, 13.75; S, 6.47; Cl, 7.29.

$C_{21}H_{29}N_5O_4S.HCl.H_2O$ requires C, 50.24; H, 6.43; N, 13.9; S, 6.38; Cl, 7.06%).

EXAMPLE 20

Analogously as described for Example 9 but using 4-(2-tert.-butoxy-ethyl)-piperidine in place of 2(S)-tert.-butoxymethyl-piperidine and using the acidolysis and work-up conditions described for Example 18 is prepared N-[4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl]-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide, m.p. 90 - 100°C. The ^{13}C -NMR spectrum is consistent with the claimed structure.

EXAMPLE 21

Analogously as described for Example 6 but using piperidin-4-yl-acetic acid ethyl ester and 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride in place of piperidin-4-yl-propionic acid methyl ester and 3-methylquinoline-8-sulfonyl chloride is prepared the crude saponification product which is chromatographed on Amberlite resin CG120 (H^+ form) (25 ml). The resin column is eluted with aqueous ethanol (1:1, by vol.) to neutral pH, then with ethanol:water:conc. ammonia (sp. gr. .880) (5:4:1, by vol.). The fractions containing the product are evaporated to give a residue which is co-evaporated (3 times) with ethanol, triturated with ether, collected by filtration, washed with ether and dried in vacuo to give (1-[5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl]-piperidin-4-yl)-acetic acid, m.p. 188-191°C. The ^{13}C -NMR spectrum is consistent with the claimed structure.

EXAMPLE 22

Analogously as described for Example 1b-c and with saponification as described for Example 3d but using acetic acid 2-piperazin-1-yl-ethyl ester hydrochloride and 5-guanidino-2(S)-naphthalenesulfonylamino-pentanoic acid is prepared naphthalene-2-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-butyl}-amide isolated as the di-hydrochloride salt after purification by gel filtration chromatography as described for Example 1c and lyophilisation of the eluate. (Found: C, 45.8; H, 6.25; N, 14.4; S, 5.5; Cl, 11.9. $C_{22}H_{32}N_6O_4S \cdot 2HCl \cdot 1.5H_2O$ requires C, 45.8; H, 6.5; N, 14.6; S, 5.6; Cl, 12.3%).

EXAMPLE 23

a) Analogously as described for Example 6a-b but using piperidin-4-ylacetic acid ethyl ester trifluoroacetate in place of piperidin-4-yl-propionic acid methyl ester is prepared {1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-acetic acid ethyl ester as a pale yellow foam, m.p. 86-95°C. The ^{13}C -NMR spectrum is consistent with the claimed structure.

b) Analogously as described for the saponification step in Example 3d but using {1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-acetic acid ethyl ester is prepared {1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-acetic acid m.p. 183-9°C. The ^{13}C -NMR spectrum is consistent with the claimed structure.

EXAMPLE 24

Analogously as described for Example 1b-c and with saponification as Example 3d but using 2-piperidin-4-yl-ethanol and 5-guanidino-2-naphthalenesulfonylamino-pentanoic acid is prepared naphthalene-2-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide isolated as the hydrochloride salt after purification by gel filtration chromatography as described for Example 1c and lyophilisation of the eluate. (Found: C, 51.0; H, 6.6; N, 13.1; S, 6.1; Cl, 6.9. $C_{23}H_{33}N_5O_4S \cdot HCl \cdot 1.5H_2O$ requires C, 51.2; H, 6.9; N, 13.0; S, 5.95; Cl, 6.6%).

EXAMPLE 25

Analogously as described for Example 1c but using (1,2,3,4-tetrahydroisoquinolin-3(RS)-yl)-methanol is prepared N-[4-guanidino-1(S)-(3(RS)-hydroxymethyl-3,4-dihydro-1.H.-isoquinoline-2-carbonyl)-butyl]-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide isolated as the acetate salt after purification by gel filtration chromatography as described for Example 1c and passage of an aqueous solution of the product through Dowex-1 (acetate form) resin and lyophilisation of the eluate. (Found: C, 59.4; H, 6.75; N, 10.1; S, 4.5. $C_{31}H_{39}N_5O_4S \cdot CH_3COOH \cdot 1.5H_2O$ requires C, 59.6; H, 7.0; N, 10.5; S, 4.8%).

EXAMPLE 26**Method 1**

a) Analogously as described for Example 3a-c but using 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride and 1-(2-benzyloxy-ethyl)-piperazine in place of 3-methylquinoline-8-sulfonyl chloride and acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared N-[4-(3-nitro-guanidino)-1(S)-[4-(2-benzyloxy-ethyl)-piperazine-1-carbonyl]-butyl]-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide.

b) N-[4-(3-Nitro-guanidino)-1(S)-[4-(2-benzyloxy-ethyl)-piperazine-1-carbonyl]-butyl]-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide (600mg) is dissolved in a mixture of methanol (37ml) and aqueous hydrochloric acid (2M, 37ml) and hydrogenated (1 bar) in the presence of 5% palladium on charcoal (10mg) for 24 hours at 30°C. After removal of catalyst, the mixture is concentrated by evaporation to give a residue which on trituration with ether gives a solid which is collected by filtration, washed with ether and dried. The solid is dissolved in water (5ml) and the solution is adjusted to pH>10 by addition of conc. ammonia (sp. gr. .880) to give a gelatinous precipitate which is dissolved by addition of dioxan. The solution obtained is evaporated to dryness and the residue triturated with ether, collected by filtration, washed with ether and dried.

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The white solid obtained is purified by chromatography on a column of silicagel using isopropanol:acetic acid: water (6:1:1, by vol.) as eluant to give N-{4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-butyl}-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide carbonate salt, isolated as the carbonate salt, m.p. 178-184°C. (Found: C, 47.8; H, 6.9; N, 12.3; S, 4.85. $C_{27}H_{40}N_6O_4S \cdot H_2CO_3 \cdot H_2O$ requires C, 48.2; H, 7.2; N, 12.5; S, 4.8%).

Method 2

Analogously as described for Example 1c but using 2-piperazin-1-yl-ethanol in place of pyrrolidin-2(R)-ylmethanol is prepared N-{4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-butyl}-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide isolated as the di-hydrochloride salt after purification by gel filtration chromatography as described for Example 1c and lyophilisation of the eluate. (Found: C, 47.8; H, 6.9; N, 12.3; S, 4.85. $C_{27}H_{40}N_6O_4S \cdot 2HCl \cdot 3H_2O$ requires C, 48.2; H, 7.2; N, 12.5; S, 4.8%).

EXAMPLE 27

Method 1

Analogously as described for Example 10 but using 4-tert.-butoxymethyl-piperidine in place of 2(R)-tert.-butoxymethyl-piperidine is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(4-hydroxymethyl-piperidine-1-carbonyl)-butyl]-amide, m.p. 104-111°C. MS(FAB) $[M+H]^+ = 481$. The ^{13}C -NMR spectrum is consistent with the claimed structure.

Method 2

Analogously as described for Example 3 but using acetic acid piperidin-4-ylmethyl ester hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(4-hydroxymethyl-piperidine-1-carbonyl)-butyl]-amide isolated as the acetate salt after passage of an aqueous solution of the product from the hydrogenation step through Dowex-1 (acetate form) resin and lyophilisation of the eluate. (Found: C, 50.9; H, 7.6; N, 13.6; S, 5.7. $C_{22}H_{36}N_6O_4S \cdot CH_3COOH \cdot 1.5H_2O$ requires C, 50.8; H, 7.6; N, 14.8; S, 5.65%).

EXAMPLE 28

Analogously as described for Example 3a-c and 3e but using tetrahydrofuran as solvent and triethylamine as the base in procedure 3a and using 2(RS)-benzyloxycarbonylaminoethyl-piperidine and 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-methylquinoline-8-sulfonyl chloride and work-up as described for Example 9 is prepared N-[1(S)-(2(RS)-aminomethyl-piperidine-1-carbonyl)-4-guanidino-butyl]-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide as a white solid, m.p. 125-132^oC (dec.). (Found: C, 58.74; H, 7.62; N, 14.56. C₂₇H₄₀N₆O₃S 1.5H₂O requires C, 58.35; H, 7.80; N, 15.12%).

EXAMPLE 29

Analogously as described for Example 10 but using 4-tert.-butoxy-piperidine in place of 2(R)-tert.-butoxymethyl-piperidine and using the acidolysis conditions described in Example 18 and omitting the basification step is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(4-hydroxy-piperidine-1-carbonyl)-butyl]-amide hydrobromide, m.p. 85-100^oC. The ¹³C-NMR spectrum is consistent with the claimed structure.

EXAMPLE 30

Analogously as described for Example 10 but using 3(R)-(2-tert.-butoxy-ethyl)-piperidine in place of 2(R)-tert.-butoxymethyl-piperidine is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[3(R)-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide, m.p. 110^oC. The ¹³C-NMR spectrum is consistent with the claimed structure.

EXAMPLE 31

Analogously as described for Examples 1b-c and 6b but using (1,2,3,4-tetrahydro-isoquinolin-3(RS)-yl)-methanol and 5-guanidino-2(S)-(3-methylquinoline-8-sulfonylamino)-pentanoic acid is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(3(RS)-hydroxymethyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)-butyl]-amide isolated as the acetate salt after passage of an aqueous solution through Dowex-1 (acetate form) resin and lyophilisation of the eluate. (Found: C, 51.9; H, 7.0; N, 13.2; S, 5.0. $C_{26}H_{35}N_6O_4S \cdot CH_3COOH \cdot 2H_2O$ requires C, 53.9; H, 6.95; N, 13.5; S, 5.1%).

EXAMPLE 32

Analogously as described for Example 6 but omitting the final addition of a calculated quantity of hydrochloric acid is prepared 3-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-propionic acid. (Found: C, 52.6; H, 7.6; N, 15.0. $C_{24}H_{38}N_6O_5S \cdot 1.5H_2O$ requires C, 52.4; H, 7.5; N, 15.3%).

EXAMPLE 33

Analogously as described for Example 10 but using 3(RS)-(3-tert.-butoxy-propyl)-piperidine in place of 2(R)-tert.-butoxymethyl-piperidine is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[3(RS)-(3-hydroxy-propyl)-piperidine-1-carbonyl]-butyl}-amide, obtained as the carbonate salt after several days' exposure to air, m.p. 90°C. (Found: C, 52.3; H, 7.6; N, 14.45. $C_{24}H_{40}N_6O_4S \cdot H_2CO_3$ requires C, 52.6; H, 7.4; N, 14.7%).

EXAMPLE 34

Analogously as described for Example 4 but using 4-(3-tert.-butoxy-propyl)-piperidine hydrochloride in place of 4-(2-tert.-butoxy-ethyl)-piperidine is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(3-hydroxy-propyl)-piperidine-1-carbonyl]-butyl}-amide, isolated as the dihydrochloride salt, m.p. 88-100°C. The ^{13}C -NMR spectrum is consistent with the claimed structure.

EXAMPLE 35

Analogously as described for Examples 3a-c and 3e but using 4-carbamoylmethylpiperidine in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-acetamide, isolated as the dihydrochloride salt, m.p. 118⁰C. (Found: C, 47.6; H, 6.9; N, 16.7; S, 5.4; Cl, 9.0. C₂₃H₃₇N₇O₄S.2HCl requires C, 47.6; H, 6.8; N, 17.0; S, 5.5; Cl, 9.2%).

EXAMPLE 36

Analogously as described for Example 1c but using 4-piperidine-ethanesulphonic acid in place of pyrrolidin-2(R)-ylmethanol is prepared 2-(1-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperidin-4-yl)-ethanesulfonic acid isolated by gel filtration chromatography as described for Example 1c and lyophilisation of the eluate. (Found: C, 53.0; H, 6.6; N, 10.7; S, 10.3. C₂₈H₄₁N₅O₆S₂.1.5H₂O requires C, 53.0; H, 7.0; N, 11.0; S, 10.1%).

EXAMPLE 37

Analogously as described for Example 3 but using quinoline-8-sulfonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride is prepared 1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide hydrochloride directly by conducting the final hydrogenation step in a mixture (1:1, by vol.) of methanol and aqueous hydrochloric acid (2M). (Found: C, 47.5; H, 7.0; N, 14.4; S, 9.3; Cl, 6.0. C₂₂H₃₆N₆O₄S.1.5HCl requires C, 47.7; H, 7.2; N, 15.2; S, 9.6; Cl, 5.8%).

EXAMPLE 38

Analogously as described for Example 3 but using succinic acid benzyl ester 2-piperidin-4-yl-ethyl ester hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared succinic acid mono-(2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl) ester directly from the hydrogenation step. (Found: C, 51.5; H, 6.4; N, 13.3; S, 4.7. $C_{27}H_{22}N_6O_7S \cdot 2H_2O$ requires C, 51.4; H, 7.3; N, 13.3; S, 5.1%).

EXAMPLE 39

Analogously as described for Example 3a-c and 3e but using N-(2-piperidin-4-yl-ethyl)-acetamide hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared N-(2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl)-acetamide obtained as the acetate salt directly from the hydrogenation step. (Found: C, 54.93; H, 7.59; N, 15.25; S, 5.07. $C_{25}H_{41}N_7O_4S \cdot 1.5CH_3COOH \cdot 1.5H_2O$ requires C, 52.98; H, 7.62; N, 15.45; S, 5.05%).

EXAMPLE 40

Analogously as described for Example 3a-c and 3e but using 4-(2-chloro-ethyl)-piperidine hydrochloride and 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-methylquinoline-8-sulfonyl chloride and the hydrogenation solvent described for Example 37 is prepared N-{1(S)-[4-(2-chloro-ethyl)-piperidine-1-carbonyl]-4-guanidino-butyl}-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide as the hydrochloride salt. (Found: C, 55.6; H, 7.0; N, 10.9; S, 5.6. $C_{28}H_{40}N_5O_5ClS \cdot HCl \cdot 1.5H_2O$ requires: C, 55.5; H, 7.3; N, 10.8; S, 5.5%).

EXAMPLE 41

Analogously as described for Example 3 but using N-(2-piperidin-4-yl-ethyl)-succinamic acid methyl ester hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared N-(2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl)-succinamic acid. (Found: C, 48.5; H, 7.59; N, 13.9; S, 4.6. $C_{27}H_{43}N_7O_6S \cdot 4H_2O$ requires C, 48.7; H, 7.7; N, 14.7; S, 4.8%).

EXAMPLE 42

Analogously as described for Example 38 but using 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride is prepared succinic acid mono-[2-(1-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl]-piperidin-4-yl)-ethyl] ester. (Found: C, 55.8; H, 7.5; N, 9.8. $C_{32}H_{45}N_5O_7S \cdot 2.5H_2O$ requires C, 55.8; H, 7.3; N, 10.2%).

EXAMPLE 43

Analogously as described for Example 38 but using 5-dimethylamino-naphthalene-1-sulfonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride is prepared succinic acid mono-(2-{1-[2(S)-(5-dimethylamino-naphthalene-1-sulfonylamino)-5-guanidino-pentanoyl]-piperidin-4-yl}-ethyl) ester. (Found: C, 53.0; H, 7.0; N, 12.6; S, 4.6. $C_{29}H_{42}N_6O_7S \cdot 2H_2O$ requires C, 53.2; H, 7.1; N, 12.8; S, 4.9%).

EXAMPLE 44

Analogously as described for Example 3 but using piperazin-1-yl-pentanoic acid ethyl ester hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 5-{4-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperazin-1-yl}-pentanoic acid acetate salt directly from the hydrogenation step. (Found: C, 47.0; H, 7.4; N, 14.4; S, 4.9. $C_{25}H_{41}N_7O_5S \cdot CH_3COOH \cdot 4H_2O$ requires C, 47.4; H, 7.8; N, 14.3; S, 4.7%).

EXAMPLE 45

Chlorocarbonyl-acetic acid benzyl ester (2.8g) and 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide hydrochloride are dissolved in dry pyridine (30ml) in a dry flask and the mixture is stirred with exclusion of moisture for 72 hours at 20°C. Solvent is removed by rotary evaporation and the residue is purified by flash chromatography on silicagel using chloroform:methanol:acetic acid (6:1:1, by vol.) as solvent to give the semi-solid benzyl ester of malonic acid (2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl) ester hydrochloride salt (2g) which is dissolved in a mixture of methanol (40ml) and acetic acid (2ml) and hydrogenated (1 bar) for 16 hours at 20°C in the presence of 10% palladium on charcoal (570mg). The catalyst is removed by filtration through a pad of Celite and the solvents removed to give a residue which is purified by preparative HPLC using chloroform:methanol:trifluoroacetic acid (390:610:1, by vol.) as solvent to afford malonic acid mono-(2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl) ester as the trifluoroacetate salt. (Found: C, 47.9; H, 6.0; N, 11.5; S, 5.0. $C_{26}H_{40}N_6O_7S.CF_3COOH.0.5H_2O$ requires C, 47.8; H, 6.0; N, 11.9; S, 4.6%).

EXAMPLE 46

Glutaric anhydride (2.3g) and 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide hydrochloride salt (2.0g) are dissolved in dry pyridine (40ml) at -20°C and stirred for 16 hours at room temperature. The reaction mixture is purified as described for the analogous Example 45 to give pentanedioic acid mono-(2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl) ester as the trifluoroacetate salt. (Found: C, 49.1; H, 6.6; N, 10.8. $C_{28}H_{44}N_6O_7S.CF_3COOH.0.5H_2O$ requires C, 49.2; H, 6.3; N, 11.5%).

EXAMPLE 47

Analogously as described for Example 3 but using 4-(2-piperidin-4-yl-ethoxy)-butyric acid ethyl ester hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 4-(2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydroquinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethoxy)-butyric acid directly from the hydrogenation step. (Found: C, 52.2; H, 7.4; N, 12.4; S, 5.0. $C_{27}H_{44}N_6O_6S \cdot 2H_2O$ requires C, 52.6; H, 7.8; N, 13.4; S, 5.2%).

EXAMPLE 48

Analogously as described for Example 3 but using 7-piperazin-1-yl-heptanoic acid ethyl ester hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 7-{4-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydroquinoline-8-sulfonylamino)-pentanoyl]-piperazin-1-yl}-heptanoic acid isolated as the acetate salt directly from the hydrogenation step. (Found: C, 46.2; H, 7.2; N, 13.2; S, 4.7. $C_{27}H_{45}N_7O_5S \cdot CH_3COOH \cdot 6H_2O$ requires C, 46.6; H, 8.2; N, 13.1; S, 4.3%).

EXAMPLE 49

Analogously as described for Example 3 but using 6-piperazin-1-yl-hexanoic acid ethyl ester hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 6-{4-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydroquinoline-8-sulfonylamino)-pentanoyl]-piperazin-1-yl}-hexanoic acid isolated as the acetate salt directly from the hydrogenation step. (Found: C, 44.99; H, 6.86; N, 12.43; S, 4.25. $C_{26}H_{43}N_7O_5S \cdot CH_3COOH \cdot 7H_2O$ requires C, 44.73; H, 8.18; N, 13.04; S, 4.25%).

EXAMPLE 50

3-Methylquinoline-8-sulfonic acid {4-(3-nitro-guanidino)-1(S)-{4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide (2.0g.) is dissolved in 2,6-lutidine (11 ml) and cooled in ice. Dibenzylphosphoryl chloride (2.4 ml) is added in two equal portions at 30 minute intervals and the reaction mixture is stirred for a further 30 minutes. Solvents are removed by rotary evaporation and the residue is held in vacuo (NaOH pellets) for 16 hours.

Purification by flash chromatography on a column of silicagel using chloroform:methanol:acetic acid (95:5:4, by vol.) affords the pure dibenzyl ester after decolourisation (charcoal) as a white foam (700mg) which is dissolved in methanol (10ml) and acetic acid (1ml) and hydrogenated (1 bar) in the presence of 10% palladium on charcoal (100mg) at 20°C for 72 hours. The catalyst is removed by filtration and the solvents by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using chloroform:methanol:conc. ammonia (sp.gr. 0.880):water (60:32:6:4, by vol.) to yield phosphoric acid mono-(2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl) ester. (Found: C, 44.14; H, 6.54; N, 14.43; S, 5.29. $C_{23}H_{39}N_6O_7SP.3H_2O$ requires C, 43.94; H, 7.21; N, 13.37; S, 5.10%).

EXAMPLE 51

Analogously as described for Example 3 but using 4-piperazin-1-yl-butyric acid ethyl ester hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 4-{4-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperazin-1-yl}-butyric acid isolated as the acetate salt directly from the hydrogenation step. (Found: C, 45.8; H, 7.1; N, 15.2; S, 4.8. $C_{24}H_{39}N_7O_5S.CH_3COOH.5H_2O$ requires C, 45.4; H, 7.8; N, 14.3; S, 4.7%).

EXAMPLE 52

Analogously as described for Example 3 but using 5-piperidin-1-yl-pentanoic acid ethyl ester hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 5-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-pentanoic acid isolated as the acetate salt directly from the hydrogenation step. (Found: C, 50.3; H, 7.3; N, 11.7; S, 4.45. $C_{26}H_{42}N_6O_5S.2CH_3COOH.2.5H_2O$ requires C, 50.3; H, 7.7; N, 11.7; S, 4.5%).

EXAMPLE 53

Analogously as described for Example 6a-b but using 2(RS)-piperidine phosphonic acid dibenzyl ester in place of 3-piperidin-4-yl-propionic acid methyl ester is prepared {1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-2(RS)-yl}-phosphonic acid directly by lyophilisation of the product recovered from the hydrogenation step. (Found: C, 45.97; H, 6.46; N, 14.77; S, 5.58. $C_{21}H_{35}N_6O_6PS \cdot H_2O$ requires C, 45.98; H, 6.80; N, 15.32; S, 5.84%).

EXAMPLE 54

3-{1-[5-Guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-propionic acid (200mg) and 3-amino-propionic acid ethyl ester hydrochloride (50mg) are added to a solution of triethylamine (90ml) in DMF (1.5ml) and stirred with DCC (75mg) and HOBt. H_2O (50mg) at 20°C for 3 hours. A further portion of DCC (75mg) is added and the mixture is stirred for 72 hours at 20°C. The mixture is filtered and the filtrate dried by rotary evaporation. The residue is dissolved in dichloromethane (10ml) and extracted with portions (10ml) of 7% aqueous citric acid, brine and saturated aqueous sodium bicarbonate, dried ($MgSO_4$) and the filtrate evaporated to give the pure ethyl ester (200mg) which is dissolved in methanol (2ml) and aqueous sodium hydroxide (M, 1.3ml) added. The mixture is stirred at 20°C for 16 hours, aqueous sulfuric acid (0.5M, 1.3ml) is added and the solution is evaporated to dryness. The residue is kept in vacuo (NaOH pellets) for 16 hours and then extracted with portions (3x10ml) of hot ethanol. Evaporation of the combined extracts gives 3-(3-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-propionylamino)-propionic acid obtained as the stable solid acetate salt by lyophilisation from dilute acetic acid solution. (Found: C, 52.6; H, 7.8; N, 14.4; S, 4.6. $C_{27}H_{43}N_7O_6S \cdot 2CH_3COOH \cdot 0.5H_2O$ requires C, 52.55; H, 7.3; N, 14.8; S, 4.8%).

EXAMPLE 55

Analogously as described for Example 3 but using 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydroquinoline-8-sulphonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide acetate salt obtained directly from the hydrogenation step as a stable solid by freeze-drying. (Found: C, 51.79; H, 7.94; N, 13.72; S, 5.5. $C_{24}H_{40}N_6O_4S \cdot CH_3COOH \cdot 2H_2O$ requires C, 51.64; H, 8.00; N, 13.90; S, 5.3%).

EXAMPLE 56

Analogously as described for Example 40 but using 3-methylquinoline 8-sulfonyl chloride in place of 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-[4-(2-chloro-ethyl)-piperidine-1-carbonyl]-4-guanidino-butyl}-amide as the hydrochloride salt. (Found: C, 48.7; H, 7.0; N, 14.85; S, 5.9. $C_{23}H_{37}N_6O_3S \cdot Cl \cdot HCl \cdot H_2O$ requires C, 48.7; H, 7.1; N, 14.8; S, 5.65%).

After passage of an aqueous solution of the compound through Dowex 1 (acetate form) resin and lyophilisation of the eluate is prepared the acetate salt. (Found: C, 44.9; H, 6.6; N, 9.7; S, 5.5; Cl, 5.5. $C_{23}H_{37}N_6O_3S \cdot Cl \cdot CH_3COOH \cdot 5H_2O$ requires C, 45.3; H, 7.7; N, 12.7; S, 4.8; Cl, 5.35%).

EXAMPLE 57

Analogously as described for Example 3 but using 3(R)-methyl-6-bromo-1,2,3,4-tetrahydroquinoliny-8-sulfonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride is prepared 3(R)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-4-guanidino-butyl}-amide acetate salt, obtained directly from the hydrogenation step, after lyophilisation, as a white solid. MS(FAB) $[M+H]^+ = 495$. The ^{13}C -NMR spectrum is consistent with the claimed structure.

EXAMPLE 58

To a stirred suspension of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(3(R)-tert.-butoxymethyl-piperidine-1-carbonyl)-butyl]-amide (268mg) in water (0.3ml) is added glacial acetic acid (3.5ml) below 15°C. When the suspension is dissolved, hydrogen bromide in acetic acid (45% w/v, 1.4ml) is added dropwise to the solution below 15°C. Stirring is continued at room temperature for 3.5 hours and the mixture is concentrated under vacuum and the residue obtained dissolved in chloroform (10ml). The solution is washed with portions of ice-cold, saturated aqueous sodium carbonate (2x5ml), saturated brine (2x5ml) and dried (MgSO₄). Solvent is evaporated to give a residue which is co-evaporated (twice) with ether to yield acetic acid 1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-3(R)-ylmethyl ester m.p. ~50° (dec). MS(FAB) [M+H]⁺ = 523. The ¹³C-NMR spectrum is consistent with the claimed structure.

EXAMPLE 59

Analogously as described for Example 58 but using 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(4-tert.-butoxymethyl-piperidine-1-carbonyl)-butyl]-amide (the last intermediate in the preparation of Example 27) in place of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(3(R)-tert.-butoxymethyl-piperidine-1-carbonyl)-butyl]-amide is prepared acetic acid 1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-ylmethyl ester, m.p. >100° (dec). MS(FAB) [M+H]⁺ = 523. The ¹³C-NMR spectrum is consistent with the claimed structure.

EXAMPLE 60

Analogously as described for Example 58 but using 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-[4-(2-tert.-butoxy-ethyl)-piperidine-1-carbonyl]-butyl]-amide (Example 4d) in place of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(3(R)-tert.-butoxymethyl-piperidine-1-carbonyl)-butyl]-amide is prepared acetic acid 2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl ester, m.p. $>70^{\circ}$ (dec). MS(FAB) $[M+H]^+ = 535$. The ^{13}C -NMR spectrum is consistent with the claimed structure.

EXAMPLE 61

Analogously as described for Example 58 but using 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(4-tert.-butoxy-piperidine-1-carbonyl)-butyl]-amide (the last intermediate in the preparation of Example 29) in place of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(3(R)-tert.-butoxymethyl-piperidine-1-carbonyl)-butyl]-amide is prepared acetic acid 1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl ester, m.p. >150 (dec). MS(FAB) $[M+H]^+ = 508.3$. The ^{13}C -NMR spectrum is consistent with the claimed structure.

EXAMPLE 62

Analogously as described for Example 58 but using 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(3(RS)-tert.-butoxy-piperidine-1-carbonyl)-butyl]-amide (the last intermediate in the preparation of Example 16) in place of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [4-guanidino-1(S)-(3(R)-tert.-butoxymethyl-piperidine-1-carbonyl)-butyl]-amide is obtained is prepared acetic acid 1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-3(RS)-yl ester $75-83^{\circ}\text{C}$. The ^{13}C -NMR spectrum is consistent with the claimed structure.

EXAMPLE 63

Analogously as described for Example 3a-c and 3e but using propionic acid piperidin-4-ylmethyl ester hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared propionic acid 1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-ylmethyl ester as the hydrochloride salt after addition of a calculated quantity of aqueous hydrochloric acid to the product obtained from the hydrogenation step and lyophilisation of the solution.

EXAMPLE 64

Analogously as described for Example 3a-c and 3e but using 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride and 4-piperidine acetic acid ethyl ester hydrochloride in place of 3-methylquinoline-8-sulfonyl chloride and acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared (1-[5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl]-piperidin-4-yl)-acetic acid ethyl ester directly from the hydrogenation step after extraction of the free base as described for Example 9.

EXAMPLE 65

Hydrogen bromide gas is bubbled for 1 hour through a solution of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-t-butoxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide acetate (Example 4d, 100mg) in propionic acid (5ml) cooled to 0-5°C and the mixture is stirred at room temperature for 3.5 hours. The mixture is concentrated by evaporation to give a residue which is triturated with ether, collected by filtration, washed with ether and dried. The solid is dissolved in chloroform (10ml) and the solution is washed with portions of ice-cold, saturated aqueous sodium carbonate (3x10ml), saturated brine (3x10ml) and dried (MgSO₄). Solvent is evaporated and the residue is dissolved in isopropanol, decolourised (charcoal), concentrated and diluted with ether to give a precipitate which is collected by filtration, washed with ether and dried in vacuo to give the product, propionic acid 2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl ester, m.p. 86-95°C. The ¹³C-NMR spectrum is consistent with the claimed structure.

EXAMPLE 66

Analogously as described for Example 3a-c and 3e but using propionic acid piperidin-4-ylmethyl ester hydrochloride and quinoline-8-sulfonyl chloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-methylquinoline-8-sulfonyl chloride is prepared propionic acid 1-[5-guanidino-2(S)-(1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-ylmethyl ester as the acetate salt after passage of an aqueous solution of the compound obtained from the hydrogenation step through a column of Dowex 1 (acetate form) resin and lyophilisation of the eluate. (Found: C, 51.43; H, 7.24; N, 13.96; S, 5.07. $C_{24}H_{38}N_6O_5S \cdot CH_3COOH \cdot 1.5H_2O$ requires C, 51.21; H, 7.44; N, 13.78; S, 5.26%).

EXAMPLE 67

Analogously as described for Example 3a-c and 3e but using propionic acid 2-piperidin-4-yl-ethyl ester hydrochloride and quinoline-8-sulfonyl chloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-methylquinoline-8-sulfonyl chloride and using the hydrogenation solvent described for Example 37 is prepared propionic acid 2-{1-[5-guanidino-2(S)-(1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl ester as the hydrochloride salt. (Found: C, 50.88; H, 7.17; N, 14.38; S, 5.43. $C_{25}H_{40}N_6O_5S \cdot HCl \cdot H_2O$ requires C, 50.79; H, 7.33; N, 14.22; S, 5.42%).

EXAMPLE 68

Analogously as described for Example 3a-c and 3e but using 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride and using the hydrogenation solvent described for Example 37 is prepared acetic acid 2-(1-[5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl]-piperidin-4-yl)-ethyl ester as the hydrochloride salt. (Found: C, 56.67; H, 7.14; N, 11.03; S, 5.44; Cl, 5.80. $C_{30}H_{43}N_5O_5S \cdot HCl \cdot 0.5H_2O$ requires C, 57.08; H, 7.19; N, 11.10; S, 5.08; Cl, 5.62%).

EXAMPLE 69

Analogously as described for Example 3a-c and 3e but using propionic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-methylquinoline-8-sulfonyl chloride and using the hydrogenation solvent described for Example 37 is prepared propionic acid 2-(1-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperidin-4-yl)-ethyl ester as the hydrochloride salt. (Found: C, 57.73; H, 7.44; N, 11.44; S, 5.08; Cl, 5.63. $C_{31}H_{45}N_5O_5S.HCl.0.5H_2O$ requires C, 58.52; H, 7.29; N, 11.01; S, 5.04; Cl, 5.57%)

EXAMPLE 70

Analogously as described for Example 3a-c and 3e but using acetic acid 2-piperazin-1-yl-ethyl ester hydrochloride and 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-methylquinoline-8-sulfonyl chloride and using the hydrogenation solvent described for Example 37 is prepared acetic acid 2-(4-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperazin-1-yl)-ethyl ester as the dihydrochloride salt. (Found: C, 48.54; H, 6.83; N, 11.71; S, 4.47. $C_{29}H_{42}N_6O_5S.2HCl.3H_2O$ requires C, 48.94; H, 6.80; N, 11.81; S, 4.51%).

EXAMPLE 71

Analogously as described for Example 3a-c and 3e but using propionic acid 2-piperazin-1-yl-ethyl ester hydrochloride and 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-methylquinoline-8-sulfonyl chloride and using the hydrogenation solvent described for Example 37 is prepared propionic acid 2-(4-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperazin-1-yl)-ethyl ester as the hydrochloride salt. (Found: C, 53.56; H, 6.97; N, 12.48; S, 5.09. $C_{30}H_{44}N_6O_5S.HCl.2H_2O$ requires C, 53.52; H, 7.34; N, 12.48; S, 4.76%).

EXAMPLE 72

Analogously as described for Example 1c but using piperazin-1-ylmethyl-phosphonic acid diethyl ester is prepared (4-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperazin-1-ylmethyl)-phosphonic acid diethyl ester hydrochloride. (Found: C, 49.62; H, 6.35; N, 11.40; S, 4.47; Cl, 4.75.

$C_{30}H_{47}N_6O_6SP.HCl.2H_2O$ requires: C, 49.82; H, 7.25; N, 11.12; S, 4.43; Cl, 4.90%).

EXAMPLE 73

Analogously as described for Example 3a-c and 3e but using quinoline-8-sulfonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride and using the hydrogenation solvent described for Example 37 is prepared acetic acid 2-{1-[5-guanidino-2(S)-(1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl ester hydrochloride. (Found: C, 51.57; H, 7.18; N, 13.64; S, 4.79.

$C_{24}H_{38}N_6O_5S.CH_3COOH.1.5H_2O$ requires C, 51.21; H, 7.44; N, 13.78; S, 5.26%).

EXAMPLE 74

(4-{5-Guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperazin-1-ylmethyl)-phosphonic acid diethyl ester hydrochloride (1.8g) is suspended in dry acetonitrile (270ml) and sodium iodide (17g) is added with vigorous stirring. Trimethylsilyl chloride (9ml) is added under an atmosphere of nitrogen and the mixture is stirred for 1 hour at 20°C. Water (50ml) is added and the solution is evaporated to half volume. Sodium thiosulphate solution is added to decolourise the mixture which is evaporated to dryness. The residue is purified by flash chromatography on a column of silicagel using chloroform:methanol (1:1, by vol.) as eluant and by preparative HPLC on Zorbax C8 resin using acetonitrile:water:trifluoroacetic acid (370:630:1, by vol.) as eluant. Recovered material is converted to the acetate salt by passage of an aqueous solution through a small column of Dowex-1 (acetate form) resin to give (4-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperazin-1-ylmethyl)-phosphonic acid acetate salt. (Found: C, 51.90; H, 6.80; N, 13.3; S, 4.90. $C_{26}H_{39}N_6O_6SP.0.5H_2O$ requires C, 51.73; H, 6.68; N, 13.92; S, 5.31%).

EXAMPLE 75

Analogously as described for Example 3a-c and 3e but using 2,2-dimethyl-propionic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3,3-dimethyl-6-chloro-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-methylquinoline-8-sulfonyl chloride is prepared 2,2-dimethyl-propionic acid 2(S)-{1-[2-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-5-guanidino-pentanoyl]-piperidin-4-yl}-ethyl ester obtained as the acetate salt directly from the hydrogenation step by lyophilisation of an aqueous solution after passage through a small column of Dowex 1 (acetate form) resin. (Found: C, 55.42; H, 8.45; N, 12.25; S, 5.47. $C_{29}H_{48}N_6O_5S \cdot CH_3COOH \cdot H_2O$ requires C, 55.50; H, 8.11; N, 12.53; S, 4.78%).

EXAMPLE 76

Analogously as described for Example 3c but using 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride is prepared acetic acid 2-{1-[5-(3-nitro-guanidino)-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl ester (2.0g) which is dissolved in a mixture of methanol (165ml) and acetic acid (16.5ml) and hydrogenated (1 bar) for 35 hours at 20°C in the presence of 10% palladium on charcoal (500mg). The catalyst is removed by filtration and the solvents by rotary evaporation to give a residue which is purified by flash chromatography on a column of silicagel using chloroform:methanol:acetic acid (60:5:10, by vol.) as eluant to give acetic acid 2-{1-[5-guanidino-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethyl ester acetate salt which is saponified as described for Example 3d to give 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide isolated as the acetate salt. (Found: C, 48.54; H, 7.18; N, 12.59. $C_{24}H_{39}N_6O_4S \cdot CH_3COOH \cdot 2.5H_2O$ requires C, 48.18; H, 7.46; N, 12.96%).

EXAMPLE 77

Analogously as described in Example 75 but using 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-6-chloro-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 2,2-dimethyl-propionic acid 2-{1-[2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-5-guanidino-pentanoyl]-piperidin-4-yl}-ethyl ester isolated as the hydrochloride salt by addition of a calculated amount of aqueous hydrochloric acid and lyophilisation of the solution. (Found: C, 53.67; H, 7.74; N, 13.36; S, 5.30. $C_{28}H_{46}N_6O_5S.HCl.0.5H_2O$ requires C, 53.87; H, 7.75; N, 13.46; S, 5.14%).

EXAMPLE 78

Analogously as described for Example 1c but using (6-piperidin-4-yl-hexyl)-phosphonic acid diethyl ester hydrochloride is prepared [6-(1-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperidin-4-yl)-hexyl]-phosphonic acid diethyl ester which is stirred in saturated hydrogen bromide in acetic acid (5ml) at 20°C for 16 hours. The solvent is removed by rotary evaporation and the residue obtained is triturated with dry ether to afford an oily solid which is purified by chromatography on a small column of Biogel-P2 resin as described for Example 1c to give [6-(1-{5-guanidino-2(S)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-pentanoyl}-piperidin-4-yl)-hexyl]-phosphonic acid hydrobromide salt. (Found: C, 47.64; H, 6.97; N, 7.40; S, 3.52; Br, 7.33. $C_{32}H_{50}N_5O_6PS.0.75HBr.4.5H_2O$ requires C, 47.70; H, 7.57; N, 8.69; S, 3.98; Br, 7.37%).

EXAMPLE 79

Analogously as described for Example 3a-c and 3e but using [2-(2-piperidin-4-yl-ethylcarbamoyl)-ethyl]-phosphonic acid diethyl ester acetate salt (513mg) in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared [2-(2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethylcarbamoyl)-ethyl]-phosphonic acid diethyl ester which is stirred in saturated hydrogen bromide in acetic acid (5ml) at 20°C for 16 hours.

The solvent is removed by rotary evaporation and the oily residue obtained is triturated with dry ether to afford a solid which is purified by gel filtration chromatography as described for Example 1c to give [2-(2-{1-[5-guanidino-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-pentanoyl]-piperidin-4-yl}-ethylcarbamoyl)-ethyl]-phosphonic acid as a solid after lyophilisation. (Found: C, 46.33; H, 6.93; N, 14.31; S, 4.54; P, 4.61. $C_{26}H_{44}N_7O_7SP \cdot 2.5H_2O$ requires C, 46.42; H, 7.04; N, 14.58; S, 4.77; P, 4.60%).

EXAMPLE 80

Analogously as described for Example 3a-c but using 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride and 4-(2-fluoro-ethyl)-piperidine hydrochloride in place of 3-methylquinoline-8-sulfonyl chloride and acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared crude 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-4-(3-nitro-guanidino)-butyl}-amide (366mg) which is dissolved in a mixture of methanol (9ml) and aqueous hydrochloric acid (M, 1ml) and hydrogenated in the presence of 10% palladium on charcoal (36mg) for 16 hours at 20°C. The catalyst is removed by filtration and the filtrate evaporated to dryness to give material which is purified by flash chromatography on a column of silicagel using chloroform:methanol:acetic acid (6:1:1, by vol.) as eluant to give, after passage of an aqueous solution of the recovered material through a column of Dowex-1 (chloride form) resin and lyophilisation of the eluate, 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-4-guanidino-butyl}-amide hydrochloride salt as a white solid. $[M+H]^+ = 544.75$. (Found: C, 47.39; H, 6.68; N, 13.04. $C_{24}H_{38}N_6O_3SFCI \cdot HCl \cdot 1.5H_2O$ requires C, 47.36; 6.96; N, 13.81%).

EXAMPLE 81

6-Chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-4-(3-nitro-guanidino)-butyl}-amide (412mg) is hydrogenated as described for Example 80 but using an increased proportion of catalyst (200mg) at 20°C for 120 hours to afford, after work-up as described for Example 80, 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-4-guanidino-butyl}-amide hydrochloride salt as a white solid. $[M+H]^+ = 511$. The ¹³C- and ¹H-NMR spectra are consistent with the claimed structure.

EXAMPLE 82

Analogously as described for Example 80 but using 4-(2,2-difluoro-ethyl)-piperidine hydrochloride in place of 4-(2-fluoro-ethyl)-piperidine hydrochloride is prepared 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-[4-(2,2-difluoro-ethyl)-piperidine-1-carbonyl]-4-guanidino-butyl}-amide, isolated as the acetate salt after the flash chromatography purification step. $[M+H]^+ = 563.25$. (Found: C, 48.03; H, 6.82; N, 12.93. C₂₄H₃₇N₆O₃SF₂Cl.CH₃COOH.1.5H₂O requires C, 48.11; 6.79; N, 13.35%).

EXAMPLE 83

Analogously as described for Example 80 but using 4-(2,2-difluoro-ethyl)-piperidine hydrochloride in place of 4-(2-fluoro-ethyl)-piperidine hydrochloride and using the hydrogenation conditions described for Example 81 is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-[4-(2,2-difluoro-ethyl)-piperidine-1-carbonyl]-4-guanidino-butyl}-amide isolated as the acetate salt after the flash chromatography purification step. $[M+H]^+ = 529.5$. (Found: C, 51.40; H, 7.42; N, 13.78. C₂₄H₃₈N₆O₃SF₂.CH₃COOH.H₂O requires C, 51.47; 7.31; N, 13.85%).

EXAMPLE 84

a) Analogously as described for Example 3a-c but using 2,2-dimethyl-propionic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3,3-dimethyl-6-chloro-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-methylquinoline-8-sulfonyl chloride is prepared 2,2-dimethyl-propionic acid 2(S)-{1-[2-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-5-(3-nitro-guanidino)-pentanoyl]-piperidin-4-yl}-ethyl ester.

b) 2,2-Dimethyl-propionic acid 2(S)-{1-[2-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-5-(3-nitro-guanidino)-pentanoyl]-piperidin-4-yl}-ethyl ester (310 mg) is hydrogenated in the presence of 10% palladium on charcoal (98mg) and 1,2-dichlorobenzene (77mg) at 20°C for 3.5 hours to give 2,2-dimethyl-propionic acid 2-{1-[2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-5-guanidino-pentanoyl]-piperidin-4-yl}-ethyl ester as the acetate salt after passage of an aqueous solution of the product through a small column of Dowex-1 (acetate form) resin and lyophilisation of the eluate. $[M+H]^+ = 627.5, 629.5$. The ^{13}C -NMR spectrum is consistent with the claimed structure.

EXAMPLE 85

Analogously as described for Example 3a-c but using 2-piperidin-4-yl-ethyl-acetamide hydrochloride and 3,3-dimethyl-6-chloro-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-methylquinoline-8-sulfonyl chloride is prepared N-(2-{1-[2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-5-(3-nitro-guanidino)-pentanoyl]-piperidin-4-yl}-ethyl)-acetamide which is hydrogenated as described for Example 3e but using hydrochloric acid in place of acetic acid and a reaction time of 8 days at 20°C to give N-(2-{1-[2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-5-guanidino-pentanoyl]-piperidin-4-yl}-ethyl)-acetamide as the hydrochloride salt directly from the hydrogenation step. $[M+H]^+ = 549.75$. The ^{13}C - and ^1H -NMR spectra are consistent with the claimed structure.

EXAMPLE 86

N-(2-{1-[2(S)-(6-Chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-5-(3-nitro-guanidino)-pentanoyl]-piperidin-4-yl}-ethyl)-acetamide is hydrogenated as described for Example 84 to give N-(2-{1-[2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-5-guanidino-pentanoyl]-piperidin-4-yl}-ethyl)-acetamide isolated as the hydrochloride salt after lyophilisation from aqueous solution. $[M+H]^+ = 584$ and 586 . The ^{13}C - and 1H -NMR spectra are consistent with the claimed structure.

EXAMPLE 87

Analogously as described for Example 3 but using 3,3-diethyl-1,2,3,4-tetrahydroquinoline-8-sulphonyl chloride in place of 3-methylquinoline-8-sulfonyl chloride is prepared 3,3-diethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {4-guanidino-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-butyl}-amide acetate salt obtained directly from the hydrogenation step as a stable solid after lyophilisation. MS(FAB) $[M+H]^+ = 538$. The ^{13}C -NMR spectrum is consistent with the claimed structure.

EXAMPLE 88

a) (R)-Cysteine (3.47g) is dissolved in aqueous sodium hydroxide solution (2M, 22ml), ethanol (24ml) is added, followed by (3-bromo-propyl)-carbamic acid benzyl ester (6.1g). The mixture is stirred for 19 hours at 20°C and evaporated to dryness. The crude 2(R)-amino-3-(3-benzyloxycarbonylamino-propylsulfanyl)-propionic acid is used directly in the next stage.

- b) The crude 2(R)-amino-3-(3-benzyloxycarbonylamino-propylsulfanyl)-propionic acid is suspended in a mixture of 50% aqueous dioxan (75ml) and aqueous sodium hydroxide solution (4M) is added dropwise to a pH of 10. Di-tert.-butyl di-carbonate (4.76g) is added in portions. The mixture is stirred at 20°C for 6 hours and the solvent evaporated. The white residue is suspended in water (100ml) and washed with ether (2x50ml). The aqueous layer is adjusted to pH2 (aqueous hydrochloric acid, M) and the solution is extracted with ethyl acetate (2x75ml). The combined organic extracts are washed with brine, dried (MgSO₄) and evaporated to yield 3-(3-benzyloxycarbonylamino-propylsulfanyl)-2(R)-tert.-butoxycarbonylamino-propionic acid as a viscous pale yellow oil.
- c) 3-(3-Benzyloxycarbonylamino-propylsulfanyl)-2(R)-tert.-butoxycarbonylamino-propionic acid (3.55g) is dissolved in dry dichloromethane (50ml) and cooled to -15°C in an acetone/dry-ice bath. NMM (1.0ml) and isobutyl chloroformate (1.1ml) are added and the mixture is stirred for 15 minutes at -15°C. Concurrently, acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride (1.79g) is dissolved in dichloromethane (50ml) and cooled to -15°C. NMM (1.0ml) is added and the mixture stirred at -15°C for 15 minutes. This mixture is slowly added to the first mixture at -15°C and the whole is stirred at -15°C for 15 minutes and then at 20°C for 3 hours. The reaction mixture is evaporated and the residue redissolved in ethyl acetate (175ml). The solution is washed with cold aqueous citric acid (7%, 2x100ml), brine (70ml), saturated aqueous sodium bicarbonate (3x70ml) and brine (2x70ml), dried (MgSO₄) and evaporated, yielding acetic acid 2-{1-[3-(3-benzyloxycarbonylamino-propylsulfanyl)-2(R)-tert.-butoxycarbonylamino-propionyl]-piperidin-4-yl}-ethyl ester as a pale yellow oil.
- d) Acetic acid 2-{1-[3-(3-benzyloxycarbonylamino-propylsulfanyl)-2(R)-tert.-butoxycarbonylamino-propionyl]-piperidin-4-yl}-ethyl ester (1.9g) is dissolved in acetic acid (10ml) with stirring. Hydrogen chloride in acetic acid (M, 3ml) is added dropwise. The mixture is stirred at 20°C for 2 hours and evaporated to yield acetic acid 2-{1-[2(R)-amino-3-(3-benzyloxycarbonylamino-propylsulfanyl)-propionyl]-piperidin-4-yl}-ethyl ester hydrochloride as a pale yellow oil.

e) Acetic acid 2-(1-[2(R)-amino-3-(3-benzyloxycarbonylamino-propylsulfanyl)-propionyl]-piperidin-4-yl)-ethyl ester hydrochloride (1.80g) is dissolved in dichloromethane (20ml) and, with stirring at 0°C, NMM (0.93ml) is added. The mixture is stirred for 10 minutes at 0°C. 3-(1-Methyl-1-phenyl-ethyl)-benzene-sulfonyl chloride (1.0g) is added to the mixture at 0°C over 2 minutes and the mixture stirred at 4°C for 16 hours. The mixture is diluted with dichloromethane (30ml) and the solution is washed with saturated aqueous sodium bicarbonate (2x10ml), water (10ml) and brine (10ml), dried (MgSO₄) and evaporated to yield the crude product as an oil which is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:1, by vol.) as eluant to give acetic acid 2-(1-[3-(3-benzyloxycarbonylamino-propylsulfanyl)-2(R)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-propionyl]-piperidin-4-yl)-ethyl ester as a yellow oil.

f) Acetic acid 2-(1-[3-(3-benzyloxycarbonylamino-propylsulfanyl)-2(R)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-propionyl]-piperidin-4-yl)-ethyl ester (1.29g) is dissolved in glacial acetic acid (4.4ml) and hydrogen bromide in acetic acid (45% w/v, 4.4ml) is added. The mixture is stirred at 20°C for 1.5 hours and evaporated to give an orange gum which is triturated with several portions of dry ether to give a yellow solid which is dried in vacuo. The residue is dissolved in saturated aqueous sodium bicarbonate (25ml) and the solution is extracted with chloroform (2x25ml). The crude hydrobromide salt (2.0g) is dissolved in aqueous sodium bicarbonate solution (50ml) and the solution is extracted with portions (2x70ml) of chloroform. The combined chloroform extracts are washed with portions (2x30ml) of aqueous hydrochloric acid (2M), dried (MgSO₄) and the solvent evaporated to give acetic acid 2-(1-[3-(3-amino-propylsulfanyl)-2(R)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-propionyl]-piperidin-4-yl)-ethyl ester hydrochloride salt. (Found: C, 54.16; H, 7.20; N, 6.26. C₃₀H₄₃N₃O₅S₂.HCl.2H₂O requires C, 54.40; H, 7.31; N, 6.34%).

EXAMPLE 89

Acetic acid 2-(1-{3-(3-amino-propylsulfanyl)-2(R)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-propionyl}-piperidin-4-yl)-ethyl ester hydrochloride salt (562mg) is dissolved in dry methanol (5ml) and sodium methoxide (649mg) is added. The mixture is kept at 0°C for 2.5 hours and acetic acid (0.69ml) is added. Solvents are removed by rotary evaporation and the mixture is purified by flash chromatography on a column of silicagel using chloroform:methanol:water:acetic acid (80:20:2:1, by vol.) as eluant to give N-{1(R)-(3-amino-propylsulfanylmethyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide, isolated as the acetic acid salt after lyophilisation. (Found: C, 60.24; H, 7.54; N, 6.51; S, 10.19. $C_{28}H_{41}N_3O_4S.CH_3COOH$ requires C, 59.28; H, 7.46; N, 6.91; S, 10.55%).

EXAMPLE 90

Analogously as described for Example 88 but using 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride is prepared acetic acid 2-(1-{3-(3-amino-propylsulfanyl)-2(R)-[3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino]-propionyl}-piperidin-4-yl)-ethyl ester. The crude hydrobromide salt (2.0g) is dissolved in saturated aqueous sodium bicarbonate solution (50ml) and the solution is extracted with portions (2x70ml) of chloroform. The combined chloroform extracts are washed with portions (2x70ml) of acetic acid (M), dried ($MgSO_4$) and the solvent evaporated. The residual oil is purified by flash chromatography on a column of silicagel using chloroform:methanol:water:acetic acid (80:20:2:1, by vol.) as eluant to give acetic acid 2-(1-{3-(3-amino-propylsulfanyl)-2(R)-[3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino]-propionyl}-piperidin-4-yl)-ethyl ester acetate salt. (Found: C, 50.60; H, 6.86; N, 8.55. $C_{25}H_{40}N_4O_5S_2.CH_3COOH.2.5H_2O$ requires C, 50.21; H, 7.65; N, 8.68%).

EXAMPLE 91

Acetic acid 2-(1-{3-(3-amino-propylsulfanyl)-2(R)-[3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino]-propionyl}-piperidin-4-yl)-ethyl ester acetate salt (188mg) is dissolved in aqueous methanol (50%, 5ml) and potassium carbonate (156mg) is added. The mixture is stirred at 20°C for 75 minutes and solvents are removed by rotary evaporation. The residue is partitioned between ethyl acetate and water (20ml of each) and the separated organic phase is dried (MgSO₄) and the solvent evaporated. Lyophilisation from dilute aqueous acetic acid solution affords N-{1(R)-(3-amino-propylsulfanylmethyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonamide, as the acetate salt. (Found: C, 49.21; H, 7.36; N, 9.03. C₂₃H₃₈N₄O₄S₂.CH₃COOH.3H₂O requires C, 49.00; H, 7.90; N, 9.14%).

EXAMPLE 92

Analogously as described for Example 88 but using 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride is prepared crude product which is purified by flash chromatography on a column of silicagel using chloroform:methanol:water:acetic acid (80:20:2:1 by vol) as eluant to yield acetic acid 2-(1-{3-(3-amino-propylsulfanyl)-2(R)-[3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino]-propionyl}-piperidin-4-yl)-ethyl ester acetate salt, obtained solid by lyophilisation from aqueous solution. (Found: C, 51.28; H, 7.64; N, 8.85. C₂₆H₄₂N₄O₅S₂.CH₃COOH.2H₂O requires C, 51.67; H, 7.74; N, 8.61%).

EXAMPLE 93

Analogously as described for Example 89 but using acetic acid 2-(1-{3-(3-amino-propylsulfanyl)-2(R)-[3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino]-propionyl}-piperidin-4-yl)-ethyl ester acetate salt in place of acetic acid 2-(1-{3-(3-amino-propylsulfanyl)-2(R)-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-propionyl}-piperidin-4-yl)-ethyl ester hydrochloride salt is prepared N-{1(R)-(3-amino-propylsulfanylmethyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonamide acetate salt. (Found: C, 51.28; H, 7.64; N, 8.85. C₂₄H₄₀N₄O₄S₂.2CH₃COOH.3.5H₂O requires C, 51.67; H, 7.74; N, 8.61%).

EXAMPLE 94

Analogously as described for Example 88c-f but using 4-(2-chloro-ethyl)-piperidine hydrochloride in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonic acid {1(R)-(3-amino-propylsulfanylmethyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide acetic acid salt, isolated by flash chromatography on a column of silicagel using chloroform:methanol:water:acetic acid (80:20:2:1, by vol.) as eluant. (Found: C, 49.03; H, 6.83; N, 8.73; S, 10.81. $C_{23}H_{37}N_4O_3S_2Cl \cdot CH_3COOH \cdot 2H_2O$ requires C, 48.97; H, 7.40; N, 9.14; S, 10.46%).

EXAMPLE 95

Analogously as described for Example 94 but using 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride is prepared crude 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(R)-(3-amino-propylsulfanylmethyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide, which is purified by flash chromatography on a column of silicagel using chloroform:methanol:water:acetic acid (80:20:2:1, by vol.) as eluant and isolated as its hydrochloride salt by addition of a calculated amount of aqueous hydrochloric acid to a solution of the acecate salt followed by lyophilisation. (Found: C, 43.49; H, 7.10; N, 8.06. $C_{24}H_{39}N_4O_3S_2Cl \cdot HCl$ requires C, 43.83; H, 7.66; N, 8.52%).

EXAMPLE 96

Analogously as described for Example 95 but using 4-(2-fluoro-ethyl)-piperidine hydrochloride in place of 4-(2-chloro-ethyl)-piperidine hydrochloride is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(R)-(3-amino-propylsulfanylmethyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide acetate salt. (Found: C, 50.90; H, 7.14; N, 9.10; S, 10.03.

$C_{24}H_{39}N_4O_3S_2F \cdot CH_3COOH \cdot 2H_2O$ requires C, 51.13; H, 7.76; N, 9.17; S, 10.50%).

EXAMPLE 97

Analogously as described for Example 88e but using 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride is prepared acetic acid 2-(1-{3-(3-benzyloxycarbonylamino-propylsulfanyl)-2(R)-[6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino]-propionyl}-piperidin-4-yl)-ethyl ester (285mg) which is dissolved in a mixture of methanol (9ml) and acetic acid (1ml) and hydrogenated in the presence of palladium on charcoal (10% w/w, 140mg) at a pressure of 1 bar at 20°C for 3 hours. Catalyst is removed by filtration and solvents by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using chloroform:methanol:water:acetic acid (80:20:2:1, by vol.) as eluant to afford acetic acid 2-(1-{3-(3-amino-propylsulfanyl)-2(R)-[6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino]-propionyl}-piperidin-4-yl)-ethyl ester as its acetate salt. (Found: C, 47.65; H, 6.58; N, 7.70; S, 8.57. $C_{26}H_{41}N_4O_5S_2Cl \cdot CH_3COOH \cdot 3H_2O$ requires C, 47.82; H, 7.31; N, 7.97; S, 9.12%).

EXAMPLE 98

Analogously as described for Example 88 but using (2-bromo-ethyl)-carbamic acid benzyl ester, 4-(2-chloro-ethyl)-piperidine hydrochloride and 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of (3-bromo-propyl)-carbamic acid benzyl ester, acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride and 3-(1-methyl)-1-phenyl-ethyl)-benzenesulfonyl chloride is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(R)-(3-amino-ethylsulfanylmethyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide, isolated as its acetate salt after purification by flash chromatography on a column of silicagel using chloroform:methanol:water:acetic acid (80:20:2:1, by vol.) as eluant. (Found: C, 47.92; H, 6.79; N, 9.60. $C_{22}H_{35}N_4O_3S_2Cl \cdot CH_3COOH \cdot 2H_2O$ requires C, 48.11; H, 7.23; N, 9.35%).

EXAMPLE 99

Analogously as described for Example 88 but using (4-bromo-butyl)-carbamic acid benzyl ester and 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of (3-bromo-propyl)-carbamic acid benzyl ester and 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride is prepared acetic acid 2-(1-{3-(4-amino-butylsulfanyl)-2(R)-[3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino]-propionyl}-piperidin-4-yl)-ethyl ester isolated as its acetate salt after purification by flash chromatography on a column of silicagel using chloroform:methanol:water:acetic acid (85:15:2:1, by vol.) as eluant. The product is an hygroscopic, off-white foamy solid after freeze drying and must be kept in vacuo (NaOH pellets). (Found: C, 52.41; H, 7.33; N, 8.71. $C_{26}H_{42}N_4O_5S_2 \cdot CH_3COOH \cdot 1.5H_2O$ requires C, 52.40; H, 7.70; N, 8.73%).

EXAMPLE 100

Analogously as described for Example 88c-e but using 3-(acetylamino-methylsulfanyl)-2(R)-tert.-butoxycarbonylamino-propionic acid and 4-(2-chloro-ethyl)-piperidine hydrochloride in place of 3-(3-benzyloxycarbonylamino-propylsulfanyl)-2(R)-tert.-butoxycarbonylamino-propionic acid and acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared N-[3-[4-(2-chloro-ethyl)-piperidin-1-yl]-2(R)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-3-oxo-propylsulfanylmethyl]-acetamide isolated after purification by flash chromatography on a column of silicagel using ethyl acetate as eluant. (Found: C, 48.31; H, 6.20; N, 9.77; S, 11.50. $C_{23}H_{35}N_4O_4S_2Cl \cdot 2H_2O$ requires C, 48.71; H, 6.93; N, 9.88; S, 11.31%).

EXAMPLE 101

Acetic acid 2-{1-[3-(3-benzyloxycarbonylamino-propylsulfanyl)-2(R)-tert.-butoxycarbonylamino-propionyl]-piperidin-4-yl}-ethyl ester (257mg) is dissolved in acetone (4ml) and hydrogen peroxide (0.13ml, 27.5% by vol.) and ammonium molybdate tetrahydrate (608mg) is added. The mixture is stirred at 20°C for 35 minutes, filtered through a plug of cotton wool to remove solids and the filtrate evaporated to dryness.

The pale yellow oil obtained is dissolved in ethyl acetate (10ml), washed with portions (2x20ml) of water, dried (MgSO_4) and the solvent evaporated to give crude material which is purified by flash chromatography on a column of silicagel using ethyl acetate:dichloromethane (1:1, by vol.) as eluant to give acetic acid 2-{1-[3-(3-benzyloxycarbonylamino-propylsulfonyl)-2(R)-tert.-butoxycarbonylamino-propionyl]-piperidin-4-yl}-ethyl ester as an oil.

b) Analogously as described for Example 88d-f but using acetic acid 2-{1-[3-(3-benzyloxycarbonylamino-propylsulfonyl)-2(R)-tert.-butoxycarbonylamino-propionyl]-piperidin-4-yl}-ethyl ester in place of acetic acid 2-{1-[3-(3-benzyloxycarbonylamino-propylsulfonyl)-2(R)-tert.-butoxycarbonylamino-propionyl]-piperidin-4-yl}-ethyl ester is prepared acetic acid 2-{1-[3-(3-amino-propane-1-sulfonyl)-2-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester acetic acid salt as a white solid obtained by lyophilisation. It has $^1\text{H-NMR}$ spectrum consistent with the claimed structure. (Found: C, 50.01; H, 7.52; N, 8.40. $\text{C}_{26}\text{H}_{42}\text{N}_4\text{O}_7\text{S}_2 \cdot \text{CH}_3\text{COOH} \cdot \text{H}_2\text{O}$ requires C, 50.58; H, 7.28; N, 8.43%).

EXAMPLE 102

a) (3-Bromo-propyl)-carbamic acid benzyl ester (1.60g) in sodium-dried ether (6ml) is added to a suspension of sodium hydride in ether (60% dispersion, 20ml) under nitrogen. The mixture is stirred for 20 minutes at 20°C and methyl iodide (1.5ml) is added. The mixture is stirred at 20°C for 2 hours, quenched with 7% aqueous citric acid (20ml) and poured into ether (10ml). The separated organic phase is washed with 7% aqueous citric acid (10ml), saturated aqueous sodium thiosulphate (10ml), brine (10ml) and dried (MgSO_4). Evaporation of solvent gives (3-bromo-propyl)-methyl-carbamic acid benzyl ester as a colourless oil which is purified by chromatography on a column of silicagel using ether:hexane (1:1, by vol.) as eluant.

b) Analogously as described for Example 88a-e but using (3-bromo-propyl)-methyl-carbamic acid benzyl ester and 3(RS)-methyl-1,2,3,4-tetrahydro-quinoliny-8-sulfonyl chloride in place of (3-bromo-propyl)-carbamic acid benzyl ester and 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride is prepared crude product which is purified by chromatography on a column of silicagel using ethyl acetate:dichloromethane (1:4, by vol.) as eluant to give the ester as a gum which is saponified as described for Example 91 to afford the alcohol as an oil. This is dissolved in water:methanol (1:2, by vol.) and converted to the acetate salt by passage through a short column of Dowex 1 (acetate form) resin. Lyophilisation gives 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-1(R)-(3-methylamino-propylsulfanylmethyl)-2-oxo-ethyl]-amide acetate salt as a pale yellow solid which is extremely hygroscopic and is stored in vacuo (NaOH pellets). (Found: C, 53.06; H, 7.57; N, 8.96; S, 10.38. $C_{24}H_{40}N_4O_4S_2 \cdot CH_3COOH \cdot H_2O$ requires C, 52.86; H, 7.85; N, 9.48; S, 10.85%).

EXAMPLE 103

Analogously as described for Example 88a but using (3-chloro-propyl)-dimethyl-amine and 3(RS)-methyl-1,2,3,4-tetrahydro-quinoliny-8-sulfonyl chloride in place of (3-bromo-propyl)-carbamic acid benzyl ester and 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride is prepared crude product as an oily residue which is purified by chromatography on a column of silicagel using chloroform:methanol (9:1, by vol) as eluant. Evaporation gives acetic acid 2-(1-{3-(3-dimethylamino-propylsulfanyl)-2(R)-[3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino]-propionyl}-piperidin-4-yl)-ethyl ester as a gum which is stored in vacuo. (Found: C, 56.27; H, 7.69; N, 9.55; S, 11.17. $C_{27}H_{44}N_4O_5S_2$ requires C, 57.01; H, 7.80; N, 9.85; S, 11.27%).

EXAMPLE 104

a) Aziridine-1,2(S)-dicarboxylic acid 1-benzyl ester 2-methyl ester (1.53g) is dissolved in chloroform (5ml) and placed under an atmosphere of nitrogen. (3-Hydroxy-propyl)-carbamic acid tert.-butyl ester (2.84g) dissolved in chloroform (5ml) is added. Boron trifluoride etherate (0.125ml) is added by syringe and the reaction is stirred under nitrogen at room temperature for 16 hours.

The solvent is removed and the residue pre-absorbed onto a column of silicagel which is eluted using ethyl acetate:hexane (2:3, by vol.) to give 2(S)-benzyloxycarbonylamino-3-(3-tert.-butoxycarbonylamino-propoxy)-propionic acid methyl ester as a clear oil.

b) 2(S)-Benzyloxycarbonylamino-3-(3-tert.-butoxycarbonylamino-propoxy)-propionic acid methyl ester (0.95g) is dissolved in methanol (10ml) and aqueous sodium hydroxide (2M, 18.2ml) is added in portions. The reaction is stirred at 20°C for 1 hour, aqueous hydrochloric acid (M, 36.4ml) is added and the solvent removed under vacuum. The residue is suspended in ethanol and stirred vigorously for an hour before filtering. The filtrate is evaporated to give 2(S)-benzyloxycarbonylamino-3-(3-tert.-butoxycarbonylamino-propoxy)-propionic acid as a white semisolid.

c) 2(S)-Benzyloxycarbonylamino-3-(3-tert.-butoxycarbonylamino-propoxy)-propionic acid (1.22g) and triethylamine (0.43ml) are dissolved in DMF (10ml) and cooled to -10°C. Isobutyl chloroformate (0.39ml) is added and the reaction is stirred at -10°C for 15 minutes. Meanwhile acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride (0.64g) is dissolved in DMF (5ml) at -10°C and triethylamine (0.43ml) is added. The mixture is added in portions over 5 minutes at this temperature to the initial reaction mixture. The pH is maintained at 9 with triethylamine and the mixture stirred at 10°C for 15 minutes before being placed in an ice/salt bath to stir for 4 hours at 0°C and then allowed to warm to room temperature. The solvent is removed and the residue is pre-absorbed onto a column of silicagel which is eluted using ethyl acetate:hexane (3:2, by vol.) to give acetic acid 2-{1-[2(S)-benzyloxycarbonylamino-3-(3-tert.-butoxycarbonylamino-propoxy)-propionyl]-piperidin-4-yl}-ethyl ester as a clear oil which is held in vacuo.

d) 2-{1-[2(S)-Benzyloxycarbonylamino-3-(3-tert.-butoxycarbonylamino-propoxy)-propionyl]-piperidin-4-yl}-ethyl ester (0.76g) is dissolved in ethanol (15ml), 10% palladium on charcoal (0.05g) is added and the mixture is hydrogenated (1 bar) at 20°C for 20 hours. After removal of the catalyst the filtrate is evaporated to give acetic acid 2-{1-[2(S)-amino-3-(3-tert.-butoxycarbonylamino-propoxy)-propionyl]-piperidin-4-yl}-ethyl ester as a clear oil.

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e) Acetic acid 2-{1-[2(S)-amino-3-(3-tert.-butoxycarbonylamino-propoxy)-propionyl]-piperidin-4-yl}-ethyl ester (0.58g) is dissolved in dichloromethane (7ml) and triethylamine (0.2ml) is added. The mixture is cooled to 0-10°C and 3-methylquinoline-8-sulfonyl chloride (0.36g) added in portions over 10 minutes. The pH is maintained at >9 and the reaction stirred for 5 hours at 10°C. The solvent is removed and the residue pre-absorbed onto a column of silicagel which is eluted with ethyl acetate:hexane (3:2, by vol.) to give acetic acid 2-{1-[3-(3-tert.-butoxycarbonylamino-propoxy)-2(S)-(3-methyl-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester as a clear oil.

f) Acetic acid 2-{1-[3-(3-tert.-butoxycarbonylamino-propoxy)-2(S)-(3-methyl-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester (0.5g) is dissolved in ethanol (10ml), and 10% palladium on charcoal (0.03g) is added, followed by aqueous hydrochloric acid (M, 0.9ml). The mixture is hydrogenated (1 bar) at 20°C for 40 hours. The catalyst is removed by filtration and the solvent evaporated to yield acetic acid 2-{1-[3-(3-tert.-butoxycarbonylamino-propoxy)-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester as a yellow oil.

g) Acetic acid 2-{1-[3-(3-tert.-butoxycarbonylamino-propoxy)-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester (0.46g) is dissolved in hydrogen chloride in acetic acid (M, 5ml) and stirred at room temperature for 1.5 hours. The solvent is removed by evaporation, and co-evaporated several times with ethanol, and the resulting yellow residual oil held under vacuum. This is pre-absorbed onto a column of silicagel which is eluted using butan-1-ol:acetic acid:water (6:1:1, by vol.) to give acetic acid 2-{1-[3-(3-amino-propoxy)-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester as the hydrochloride salt. It is an oil/semi-solid. (Found: C, 52.23; H, 7.45; N, 8.72. C₂₅H₄₀N₄O₆S.HCl.H₂O requires C, 51.85; H, 7.85; N, 7.48%).

EXAMPLE 105

Analogously as described for Example 104 but using (4-hydroxy-butyl)-carbamic acid tert.-butyl ester in place of (3-hydroxy-propyl)-carbamic acid tert.-butyl ester is prepared acetic acid 2-{1-[3-(4-amino-butoxy)-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester isolated as its acetate salt after chromatography on a column of silicagel using chloroform:methanol:acetic acid (6:1:1, by vol.) as eluant. $[M+H]^+ = 539$.

EXAMPLE 106

Analogously as described for Example 90 but using (RS)-homocysteine and (2-bromo-ethyl)-carbamic acid benzyl ester in place of (R)-cysteine and (3-bromo-propyl)-carbamic acid benzyl ester (Example 88a) is prepared acetic acid 2-{1-[4-(2-amino-ethylsulfanyl)-2(RS)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-butyryl]-piperidin-4-yl}-ethyl ester. The ^{13}C -NMR spectrum is consistent with the claimed structure. $[M+H]^+ = 542$.

EXAMPLE 107

a) 3-Amino-propyl)-carbamic acid benzyl ester (3.52g) is suspended in ethanol (100ml) and aqueous sodium hydroxide (4M, 4.25ml) is added. The mixture is stirred for 3 hours and the precipitated sodium chloride is removed by filtration. The filtrate is evaporated and the residue suspended in acetonitrile (150ml). (2-Oxo-oxetan-3(S)-yl)-carbamic acid tert.-butyl ester (1.58g) is dissolved in acetonitrile (150ml) and added dropwise over 1 hour and the mixture is stirred for 16 hours at 20°C, filtered and the filtrate evaporated to dryness. The resulting white foam is pre-absorbed onto a column of silicagel and eluted with chloroform:methanol:acetic acid (12:1:1, by vol.) to give 3-(3-benzyloxycarbonylamino-propylamino)-2(S)-tert.-butoxycarbonylamino-propionic acid, obtained as a white solid after lyophilisation from aqueous solution.

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b) 3-(3-Benzylloxycarbonylamino-propylamino)-2-tert.-butoxycarbonylamino-propionic acid (1.7g), Huenig Base (2.04ml) and acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride (0.98g) are dissolved in dichloromethane (85ml) and PyBOP (2.24g) is added. The mixture is stirred at 20°C for 16 hours and solvents are removed by rotary evaporation. The residue is dissolved in ethyl acetate (50ml) and extracted with portions (25ml) of aqueous citric acid (10% by wt., x2), brine, saturated aqueous sodium bicarbonate (x2) and brine, dried (MgSO₄) and solvent evaporated to give an orange oil which is purified by chromatography on a column of silicagel by elution with methanol:chloroform (1:19, by vol.) to give acetic acid 2-{1-[3-(3-benzylloxycarbonylamino-propylamino)-2(S)-tert.-butoxycarbonylamino-propionyl]-piperidin-4-yl}-ethyl ester as a light yellow oil which is kept in vacuo.

c) Acetic acid 2-{1-[3-(3-benzylloxycarbonylamino-propylamino)-2(S)-tert.-butoxycarbonylamino-propionyl]-piperidin-4-yl}-ethyl ester (1.22g) is dissolved in hydrogen chloride in acetic acid (M, 15ml) and the mixture is stirred at room temperature for 1 hour. Solvents are removed by rotary evaporation to give acetic acid 2-{1-[2(S)-amino-3-(3-benzylloxycarbonylamino-propylamino)-propionyl]-piperidin-4-yl}-ethyl ester hydrochloride as a yellow oil which is held in vacuo (NaOH pellets).

d) Acetic acid 2-{1-[2(S)-amino-3-(3-benzylloxycarbonylamino-propylamino)-propionyl]-piperidin-4-yl}-ethyl ester hydrochloride (1.33g) is dissolved in dichloromethane (10ml) at 0°C and NMM (1.5ml) is added. 3,3-Dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride (0.57g) dissolved in dichloromethane (15ml) at 0°C is added over 5 minutes, assuring the pH of the mixture remains above 9, and the mixture is stirred for 16 hours, allowing to come to room temperature. Solvents are removed by rotary evaporation and the residue is purified by chromatography on a column of silicagel which is eluted with ethyl acetate to give acetic acid 2-{1-[3-(3-benzylloxycarbonylamino-propylamino)-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester as a white foam after evaporation from ethanol:diethyl ether (1:1, by vol.).

e) Acetic acid 2-{1-[3-(3-benzyloxycarbonylamino-propylamino)-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester (0.66g) is dissolved in methanol (10ml) and hydrogenated (1 bar) in the presence of 10% palladium on charcoal (65mg) for 16 hours at 20°C. After removal of catalyst and solvent, the residue is purified by chromatography on a column of silicagel eluted with chloroform:methanol:acetic acid (6:1:1, by vol.) to give acetic acid 2-{1-[3-(3-amino-propylamino)-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester acetate salt as a white foam after evaporation from ethanol:diethyl ether (1:1, by vol.).

f) Acetic acid 2-{1-[3-(3-amino-propylamino)-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester acetate salt (0.37g) is dissolved in ethanol (7ml) and aqueous sodium hydroxide (M, 2.58ml) is added. The mixture is stirred at 20°C for 16 hours, aqueous hydrochloric acid (M, 3ml) is added and solvents are removed by rotary evaporation. The residue is extracted with several portions of ethanol and the combined extracts are evaporated from ethanolic solution several times to give an oil which affords 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-[(3-amino-propylamino)-methyl]-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide mixed acetate/hydrochloride salt as a white foam on evaporation from ether. (Found: C, 50.58; H, 7.59; N, 10.84; S, 5.41; Cl, 3.61. $C_{24}H_{41}N_5O_4S_2 \cdot 2CH_3COOH \cdot 0.75HCl \cdot H_2O$ requires C, 50.87; H, 7.59; N, 10.59; S, 4.85; Cl, 4.02%).

EXAMPLE 108

a) 2(S)-Benzyloxycarbonylamino-3-benzothiazol-2-yl-propionic acid benzyl ester (10g) is dissolved in THF (60ml) and water (20ml), lithium hydroxide monohydrate (1.85g) and aqueous hydrogen peroxide (27.5%, 16ml) are added. The solution is kept at 20°C for 1 hour and sodium sulfite (17g) in water (50ml) is added slowly to the stirred mixture in an ice-bath. The solution is acidified to pH4 (conc. aqueous hydrochloric acid) and extracted with ethyl acetate (2x25ml). The combined organic extracts are washed with brine (50ml), dried ($MgSO_4$) and evaporated to dryness. The residue is triturated with ether (50ml) to afford 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-propionic acid as white crystals which are recrystallised from acetonitrile or tert-butylmethylether.

b) 1-(2-Fluoro-ethyl)-piperazine hydrochloride (1.27g), 2(S)-benzyloxy-carbonylamino-3-benzothiazol-2-yl-propionic acid (2.70g) and PyBOP (3.93g) are dissolved in dry dichloromethane (100ml) and cooled in an ice-salt bath. Huenig base (2.44g) is added and the reaction mixture is stirred for 16 hours at 20°C. The solvent is removed by evaporation and the residue dissolved in ethyl acetate, washed with portions (50ml) of cold 10% aqueous citric acid, saturated aqueous sodium bicarbonate and brine. The organic phase is dried (MgSO_4), filtered and evaporated to dryness. Chromatography on a column of silicagel, using ethanol:ethyl acetate (1:9, by vol.) as eluant, gives pure 2(S)-benzyloxycarbonyl-amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperazin-1-yl]-propan-1-one as a pale yellow oil.

c) A solution of 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperazin-1-yl]-propan-1-one (1.64g) in glacial acetic acid (4.65ml) is stirred with HBr in acetic acid (45% w/v, 9.3ml) for 2 hours at 20°C. The solvent is removed by rotary evaporation and the residue washed with diethylether (2x30ml). The pure 2(S)-amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperazin-1-yl]-propan-1-one dihydrobromide is held in vacuo (NaOH pellets) as a colourless solid.

d) To a cooled solution of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8- sulfonyl chloride (0.62g) and 2(S)-amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperazin-1-yl]-propan-1-one dihydrobromide (1.087g) in dry dichloromethane (15ml) at -20°C, triethylamine (1.6ml) is added so that the pH of the reaction mixture is >9.0. The reaction mixture is stirred for 16 hours at 20°C and evaporated to dryness. The residue is dissolved in ethyl acetate (100ml) and washed with portions (25ml) of cold 10% aqueous citric acid, saturated aqueous sodium bicarbonate, brine, dried (MgSO_4), filtered and evaporated to dryness. Chromatography on a column of silicagel using ethanol:ethylacetate (1:19, by vol.) as eluant gives pure 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperazine-1-carbonyl]-ethyl}-amide as a colourless glass. (Found: C, 57.69; H, 6.19; N, 12.29, S, 11.32; F, 3.55. $\text{C}_{27}\text{H}_{34}\text{N}_5\text{O}_3\text{S}_2\text{F}$ requires C, 57.94; H, 6.12; N, 12.51, S, 11.46, F, 3.39%).

EXAMPLE 109

- a) 2(S)-Amino-3-benzothiazol-2-yl-propionic acid hydrobromide (406mg) and triethylamine (781 μ l) are dissolved in dichloromethane (10ml), 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride (362mg) is added and the mixture is stirred at 20°C for 2 hours. The solution is evaporated to dryness, the residue dissolved in ethyl acetate (10ml) and the solution extracted with portions (10ml) of aqueous hydrochloric acid (M, 2x), water and brine, dried (MgSO₄) and the solution evaporated to dryness. Trituration of the residue with ethyl acetate (5ml) gives 3-benzothiazol-2-yl-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionic acid as brown crystals.
- b) 3-Benzothiazol-2-yl-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionic acid (200mg), Huenig base (202 μ l), PyBOP (253mg) and acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride (96mg) are dissolved in dichloromethane (10ml) and the solution is stirred for 16 hours at 20°C. The solution is diluted with ethyl acetate (25ml) and extracted at 0°C with portions (25ml) of aqueous hydrochloric acid (0.1M, 3x), brine (2x), saturated aqueous sodium bicarbonate (3x) and brine, dried (MgSO₄) and evaporated to dryness to give a residue which is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:1, by vol.) as eluant to give acetic acid 2-{1-[3-benzothiazol-2-yl-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester as a colourless foam.
- c) Acetic acid 2-{1-[3-benzothiazol-2-yl-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester (170mg) is dissolved in methanol (3ml) and aqueous sodium hydroxide (M, 268 μ l) is added. The mixture is stirred at 20°C for 16 hours and evaporated to dryness. The residue is dissolved in ethyl acetate (5ml), the solution is washed with portions (5ml) of water (x2) and brine, dried (MgSO₄) and evaporated to give 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a solid after freeze-drying. It has a 1H-NMR spectrum consistent with the claimed structure. [M+H]⁺ = 592, 594.

EXAMPLE 110

- a) Analogously as described for Example 108b but using 4-(2-fluoro-ethyl)-piperidine hydrochloride in place of 1-(2-fluoro-ethyl)-piperazine hydrochloride is prepared 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one.
- b) A solution of 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one (1.64g) in glacial acetic acid (11.4ml) is stirred with hydrogen bromide in acetic acid (33% w/v, 4.2ml) for 4 hours at 20°C. *tert.*-Butylmethylether (75ml) is added and the mixture is stirred under nitrogen for 18 hours, the crystalline precipitate filtered off and washed with a little *tert.*-butylmethylether and triturated with diethyl ether (15ml) to give 2(S)-amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one dihydrobromide which is dried at 45°C for 18 hours in vacuo over phosphorus pentoxide and sodium hydroxide pellets. (Found C, 41.03; H, 5.13; N, 7.85; F, 3.75. $C_{17}H_{22}FN_3OS \cdot 2HBr$ requires C, 41.06; H, 4.86; N, 8.45; F, 3.82%).
- c) Analogously as described for Example 108d but using 2(S)-amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one dihydrobromide and 8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester in place of 2(S)-amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperazin-1-yl]-propan-1-one dihydrobromide and 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared prepared 8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester. After purification by flash chromatography on a column of silicagel using dichloromethane:ether (20:1 then 9:1, by vol.) as eluant and evaporation of the solvent, it is obtained as a colourless foam. It has 1H - and ^{13}C -NMR spectra consistent with the claimed structure.
- d) 8-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester (100mg) is dissolved in methanol (2ml) and aqueous sodium hydroxide (M, 1.267ml) is added. The mixture is stirred for 80 hours at 20°C, evaporated and the residue dissolved in water (10ml).

The solution is extracted with ether (3x10ml), acidified to pH2 (M aqueous hydrochloric acid) and the solution is extracted with ethyl acetate (3x10ml). The combined organic extracts are dried (MgSO₄) and evaporated to give cream crystals. The product is isolated by flash column chromatography on a column of silicagel using dichloromethane:methanol (96:4, by vol.) as eluant. Evaporation of appropriate fractions of the eluate affords 8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid as a white solid. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 603.6.

EXAMPLE 111

a) 2(S)-tert.-Butoxycarbonylamino-succinic acid 1-methyl ester (2.54g) is dissolved in toluene (50ml) and Lawesson's Reagent (2.18g) is added. The mixture is warmed to 80°C for 30 minutes. The solvent is removed in vacuo to give a brown residue which is purified by flash chromatography on a column of silicagel, eluting with dichloromethane:ethyl acetate (9:1, 8:1 and then 1:1, by vol.). Concentration of the relevant fractions produces 2(S)-tert.-butoxycarbonylamino-3-thiocarbamoyl-propionic acid methyl ester as a pale brown oil.

b) 2(S)-tert.-Butoxycarbonylamino-3-thiocarbamoyl-propionic acid methyl ester (2.14g) is dissolved in dry THF (20ml) and molecular sieves (4 Angstroms) are added to the solution which is placed under an atmosphere of nitrogen. 1,3-Dichloroacetone (1.19g) is added and the mixture is stirred for 48 hours at 20°C. The mixture is diluted with ethyl acetate (70ml) and washed with 10% aqueous sodium bicarbonate (50ml). The organic layer is separated, dried (MgSO₄), filtered and concentrated in vacuo to give the crude product which is purified by flash chromatography on a column of silicagel, eluting with ethyl acetate:dichloromethane (1:9 then 1:4, by vol.). Concentration of the relevant fractions gives 2(S)-tert.-butoxy-carbonylamino-3-(4-chloromethyl-thiazol-2-yl)-propionic acid methyl ester as a pale yellow oil.

c) 2(S)-tert.-Butoxycarbonylamino-3-(4-chloromethyl-thiazol-2-yl)-propionic acid methyl ester (1.97g) is dissolved in ethanol (20ml) and aqueous potassium hydroxide (M, 6.0ml) is added to the stirred solution at 20°C. Addition of the base initially imparts a red colour to the reaction mixture which quickly subsides to give an opaque solution. After 1 hour the reaction solution is concentrated in vacuo and the residue dissolved in water (30ml). The solution is washed with ethyl acetate (30ml). The separated aqueous layer is acidified to pH3 by the careful addition of aqueous hydrochloric acid (M) and the product extracted with ethyl acetate (3x30ml). The combined organic extracts are washed with brine, filtered, dried (MgSO₄) and concentrated in vacuo to yield pure 2(S)-tert.-butoxycarbonylamino-3-(4-chloromethyl-thiazol-2-yl)-propionic acid as a colourless solid.

d) 2(S)-tert.-Butoxycarbonylamino-3-(4-chloromethyl-thiazol-2-yl)-propionic acid (510mg) is dissolved in dichloromethane (20ml) and acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride (910mg), PyBOP (910mg) and Huenig Base (0.82ml) are added to the solution. The mixture is stirred at 20°C for 16 hours. The solution is washed with portions (20ml) of 10% aqueous citric acid, 10% aqueous sodium bicarbonate and saturated brine. The dichloromethane phase is dried (MgSO₄) and concentrated in vacuo to give the crude product which is purified by flash chromatography on a column of silicagel to give pure acetic acid 2-{1-[2(S)-tert.-butyloxycarbonyl-amino-3-(4-chloromethyl-thiazol-2-yl)-propionyl]-piperidin-4-yl}-ethyl ester as a white foam.

e) (i) Acetic acid 2-{1-[2(S)-tert.-butoxycarbonylamino-3-(4-chloromethyl-thiazol-2-yl)-propionyl]-piperidin-4-yl}-ethyl ester (822mg) is stirred with hydrogen chloride in acetic acid (M, 6ml) for 16 hours under a nitrogen atmosphere at 20°C. The acetic acid is removed in vacuo to give acetic acid 2-{1-[2(S)-amino-3-(4-chloromethyl-thiazol-2-yl)-propionyl]-piperidin-4-yl}-ethyl ester hydrochloride which is used in the crude state.

(ii) Acetic acid 2-{1-[2(S)-amino-3-(4-chloromethyl-thiazol-2-yl)-propionyl]-piperidin-4-yl}-ethyl ester hydrochloride is dissolved in dichloromethane (5ml) and sufficient Huenig Base (>0.29ml) is added to the solution to raise the pH to 9. 3,3-Dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride (445mg) is added to the solution which is stirred at 20°C for 5 hours.

The solution is washed with 10% aqueous citric acid (2x20ml) and saturated brine, the dichloromethane phase dried (MgSO_4), filtered and concentrated in vacuo to give crude product as a brown foam which is purified by flash chromatography on a column of silicagel, eluting with ethyl acetate:dichloromethane (1:4, by vol.) to give 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-(4-chloromethyl-thiazol-2-ylmethyl)-2-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a pale cream foam.

f) 3,3-Dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-(4-chloromethyl-thiazol-2-ylmethyl)-2-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (240mg) is dissolved in ethanol (20ml) and aqueous sodium hydroxide (M, 1.2ml) is added. The mixture is stirred for 30 minutes at 20°C, concentrated in vacuo and the residue dissolved in water (20 ml). The solution is extracted with dichloromethane (2x20ml) and the combined organic extracts are washed with brine, dried (MgSO_4) and concentrated to give 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-(4-chloromethyl-thiazol-2-ylmethyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a white foam which requires no further purification.

g) 3,3-Dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-(4-chloromethyl-thiazol-2-ylmethyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (150mg) is dissolved in DMF (5ml) and sodium azide (20mg) and a catalytic amount of sodium iodide (3mg) are added to the solution at 80°C. The mixture is stirred at 80°C for 1 hour and concentrated to give a residue which is dissolved in water (30ml). The solution is extracted with ethyl acetate (2x30ml) and the combined extracts washed with brine, dried (MgSO_4) and concentrated to give 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-(4-azidomethyl-thiazol-2-ylmethyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a pale yellow sticky foam.

h) To a solution of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-(4-azidomethyl-thiazol-2-ylmethyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide in THF (2ml) is added triphenylphosphine (38mg) and water (2ml). The mixture is stirred at 20°C for 16 hours and concentrated to give a residue which is dissolved in chloroform:methanol:acetic acid (6:1:1, by vol.) and purified by flash chromatography on a column of silicagel using the same solvent mixture.

The relevant fractions are pooled and concentrated to afford 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid ((1S)-(4-aminomethyl-thiazol-2-ylmethyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl)-amide as a colourless crystalline solid. The product is converted to the acetate salt by passage of an aqueous solution through a column of Dowex-1 (acetate form) resin and freeze-drying of the eluate. It has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 537.2$.

EXAMPLE 112

a) 2(S)-tert.-Butoxycarbonylamino-succinic acid 4-benzyl ester (3.23g), acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride (2.28g), PyBOP (6.24g) and Huenig Base (3.49ml) are dissolved in dichloromethane (100ml) and the mixture stirred for 16 hours at 20°C. The mixture is diluted with ethyl acetate (300ml), extracted with portions (3x100ml) of water and saturated aqueous sodium bicarbonate, the organic phase is dried (MgSO_4), evaporated and the residue purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:1, by vol.) as eluant to give [1-2(S)-tert.-butoxycarbonylamino-succinyl-4-(2-acetoxy-ethyl)]-piperidine as a colourless oil.

b) [1-2(S)-tert.-Butoxycarbonylamino-succinyl]-4-(2-acetoxy-ethyl)-piperidine (4.8g) is dissolved in dichloromethane (50ml) and trifluoro-acetic acid (7ml) is added. The mixture is stirred for 4 hours at 20°C and the mixture evaporated to give a pink oil. This is dissolved in ethyl acetate (50ml) and the solution extracted with saturated aqueous sodium bicarbonate (2x25ml). The organic layer is dried (MgSO_4) and evaporated to give 4-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-3(S)-amino-4-oxo-butyric acid benzyl ester as a brown oil.

c) Triethylamine (2.15ml) is added to 4-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-3(S)-amino-4-oxo-butyric acid benzyl ester (2.9g) dissolved in dichloromethane (50ml), 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride (2.35g) is added and the mixture is stirred for 16 hours at 20°C. The solution is evaporated, the residue is dissolved in ethyl acetate (50ml) and the solution is extracted with portions (20ml) of water (2x) and brine.

The combined aqueous extracts are washed with ethyl acetate and the combined organic phases are dried (MgSO_4), evaporated and purified by flash chromatography on a column of silicagel using ethyl acetate as eluant to give 4-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-3(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-4-oxo-butyric acid benzyl ester as a white foam.

d) Triethylamine (1.76ml) is added to a solution of 4-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-3(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-4-oxo-butyric acid benzyl ester (1.9g) in methanol (25ml) and 10% palladium on charcoal (400mg) is added. The mixture is hydrogenated (1 atm.) for 4 hours at 20°C. The catalyst is removed by filtration and the filtrate is evaporated to give a residue which is dissolved in ethyl acetate (25ml), washed with portions (15ml) of aqueous hydrochloric acid (M), water, brine, dried (MgSO_4) and evaporated to give 4-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-3(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-4-oxo-butyric acid (containing a trace of the dechlorinated product) as a white foam.

e) Triethylamine (140 μl) is added to a solution of 4-[4-(2-acetoxy-ethyl)-piperidin-1-yl]-3(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-4-oxo-butyric acid (544mg) dissolved in THF (8ml). The solution is cooled to -10°C and isobutylchloroformate (0.13ml) is added. After 10 minutes a solution of 1,2-phenylenediamine (120mg) in THF (2ml) is added. The suspension is stirred at 20°C for 4 hours, the mixture is evaporated and the residue dissolved in ethyl acetate (10ml), extracted with portions (10ml) of water, saturated aqueous sodium bicarbonate (2x) and brine. The organic phase is dried (MgSO_4) and evaporated and the residue purified by flash chromatography on a column of silicagel using methanol:dichloromethane (1:49, by vol.) to give a yellow foam. This foam (320mg) is dissolved in acetic acid (10ml) and stirred for 16 hours at 80°C. The yellow solution is evaporated, dissolved in ethyl acetate (10ml) and the solution is washed with portions (10ml) of saturated aqueous sodium bicarbonate, water and brine. The organic phase is dried (MgSO_4) and evaporated to give a residue which is purified by flash chromatography on a column of silica gel using ethyl acetate as eluant to give acetic acid 2-{1-[3-(1H-benzoimidazol-2-yl)-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester as a white foam.

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f) Acetic acid 2-{1-[3-(1H-benzoimidazol-2-yl)-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester (160mg) is dissolved in methanol (2ml) and aqueous sodium hydroxide (2M, 0.26ml) is added. The solution is stirred for 16 hours at 20°C, evaporated and the residue dissolved in ethyl acetate (10ml). The solution is washed with portions (10ml) of water and brine. The organic phase is dried (MgSO_4), evaporated and purified by flash chromatography on a column of silicagel using methanol:dichloromethane (1:19, by vol.) as eluant to give the crude product as a white foam. Purification by preparative HPLC on a column of Nucleosil-10C₁₈ using a gradient (from 300:700:1 to 550:450:1, by vol.) of acetonitrile:water:trifluoroacetic acid as eluant gives 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-(1H-benzoimidazol-2-ylmethyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as the trifluoroacetate salt which has a ¹³C-NMR spectrum consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 574, 576$.

EXAMPLE 113

a) By the procedure described in Example 109 but using 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-ethyl}-amide which has a ¹³C-NMR spectrum consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 558$.

b) Chloromethylmethylether (14.5μl) is added over 2 minutes to a solution of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-ethyl}-amide (50mg) in dichloromethane (3ml) containing Huenig Base (61μl) at 0°C under N₂. After 3 hours, further portions of chloromethylmethylether (7μl) and Huenig Base (30μl) are added and the mixture is stirred at 0°C for a further 1.5 hours. Ethyl acetate (10ml) is added and the mixture is washed with portions (5ml) of saturated aqueous sodium bicarbonate, brine, dried (MgSO_4) and concentrated in vacuo. The residue is purified by chromatography on a column of silicagel using ethyl acetate:hexane (1:1, by vol.) as eluant to give 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-methoxymethoxy-ethyl)-piperidine-1-carbonyl]-ethyl}-amide as a white foam. (Found C, 59.71, H, 6.82; N, 9.11. C₃₀H₄₀N₄O₅S₂ requires C, 59.97; H, 6.71; N, 9.32%).

EXAMPLE 114

Analogously as described for Example 111b-e but using chloroacetone in place of 1,3-dichloroacetone and 6-chloro-3,3-dimethyl-1,2,3,4-tetra-hydro-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is obtained acetic acid 2-{1(S)-[2-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-3-(4-methyl-thiazol-2-yl)-propionyl]-piperidin-4-yl}-ethyl ester as a pale cream foam. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. $[M+H]^+ = 597, 599$.

EXAMPLE 115

Analogously as described for Example 111b-f but using bromoacetophenone in place of 1,3-dichloroacetone is obtained 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-2-(4-phenyl-thiazol-2-yl)-ethyl]-amide. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. (Found: C, 61.97; H, 6.69; N, 9.64. C₃₀H₃₇N₄O₄S₂ requires C, 61.94; H, 6.41; N, 9.63%).

EXAMPLE 116

Analogously as described for Example 108d but using 3,3-diethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 3,3-diethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperazine-1-carbonyl]-ethyl}-amide as a colourless foam. (Found: C, 59.19; H, 6.44; N, 11.82. C₂₈H₃₈N₅O₃FS₂ requires C, 59.26; H, 6.52; N, 11.92%).

EXAMPLE 117

Analogously as described for Example 111b-e but using chloroacetone in place of 1,3-dichloroacetone and saponifying as described for Example 109c is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-1(S)-(4-methyl-thiazol-2-ylmethyl)-2-oxo-ethyl]-amide. (Found: C, 57.34; H, 7.07; N, 10.57; S, 12.54. $C_{25}H_{36}N_4O_4S_2$ requires C, 57.67; H, 6.97; N, 10.76; S, 12.32%).

EXAMPLE 118

a) Analogously as described for Example 108 but using 2(S)-benzyloxycarbonylamino-3-benzooxazol-2-yl-propionic acid hydrobromide in place of 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-propionic acid hydrobromide, 3-methyl-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride and acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride in place of 4-(2-fluoro-ethyl)-piperazine hydrochloride is prepared acetic acid 2-{1-[3-benzooxazol-2-yl-2(S)-(3-methyl-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester.

EXAMPLE 119

Acetic acid 2-{1-[3-benzooxazol-2-yl-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester is treated as described in Example 109c to give 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzooxazol-2-yl-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-ethyl}-amide. (Found: C, 61.29; H, 6.80; N, 10.46; S, 5.93. $C_{27}H_{34}N_4O_5S$ requires C, 61.58; H, 6.51; N, 10.64; S, 6.09%).

EXAMPLE 120

Analogously as described for Example 108 but using 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride and acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride in place of 4-(2-fluoro-ethyl)-piperazine hydrochloride is prepared acetic acid 2-{1-[3-benzothiazol-2-yl-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester. (Found: C, 59.44; H, 5.96; N, 9.48; S, 10.93. $C_{29}H_{36}N_4O_5S_2$ requires C, 59.57; H, 6.21; N, 9.58; S, 10.97%).

EXAMPLE 121

By the procedure described in Example 109c, acetic acid 2-{1-[3-benzothiazol-2-yl-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl-amino)-propionyl]-piperidin-4-yl}-ethyl ester is converted to 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-ethyl}-amide. (Found: C, 58.78; H, 6.28; N, 9.56; S, 11.56. $C_{27}H_{34}N_4O_4S_2$ requires C, 58.78; H, 6.39; N, 10.15; S, 11.62%).

EXAMPLE 122

Analogously as described for Example 108 but using 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride and 4-propyl-piperidine in place of 1-(2-fluoro-ethyl)-piperazine is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [2-benzothiazol-2-yl-1(S)-(4-propyl-piperidine-1-carbonyl)-ethyl]-amide. (Found: C, 62.18; H, 7.08; N, 10.25; S, 11.93. $C_{28}H_{36}N_4O_3S_2$ requires C, 62.19; H, 6.71; N, 10.36; S, 11.86%).

EXAMPLE 123

Analogously as described for Example 108 but using 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride and 4-(2-chloro-ethyl)-piperidine hydrochloride in place of 1-(2-fluoro-ethyl)-piperazine hydrochloride is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-chloro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide. (Found: C, 57.60; H, 5.85; N, 10.13; S, 11.78; Cl, 6.46. $C_{27}H_{33}N_4O_3S_2Cl$ requires C, 57.79; H, 5.93; N, 9.98; S, 11.43; Cl, 6.32%).

EXAMPLE 124

Analogously as described for Example 122 but using 4-ethyl-piperidine in place of 4-propyl-piperidine is prepared is 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [2-benzothiazol-2-yl-1(S)-(4-ethyl-piperidine-1-carbonyl)-ethyl]-amide. (Found: C, 61.31; H, 6.83; N, 10.41; S, 12.37. $C_{27}H_{34}N_4O_3S_2$ requires C, 61.57; H, 6.51; N, 10.64; S, 12.18%).

EXAMPLE 125

Analogously as described for Example 123 but using 4-(2-bromo-ethyl)-piperidine hydrobromide in place of 4-(2-chloro-ethyl)-piperidine hydrochloride is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-bromo-ethyl)-piperidine-1-carbonyl]-ethyl}-amide. (Found: C, 53.87; H, 5.55; N, 9.02; S, 10.53; Br, 13.24; $C_{27}H_{33}N_4O_3S_2Br$ requires C, 53.55; H, 5.49; N, 9.25; S, 10.59; Br, 13.19%).

EXAMPLE 126

Analogously as described for Example 123 but using 4-(2-fluoro-ethyl)-piperidine in place of 4-(2-chloro-ethyl)-piperidine hydrochloride is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide. The crude product is purified by preparative HPLC on a column of Zorbax-C8 using acetonitrile:water:trifluoroacetic acid (600:400:1, by vol.) as eluant to give the pure product which has a ¹³C-NMR spectrum consistent with the claimed structure. [M+H]⁺ = 544.

EXAMPLE 127

Analogously as described for Example 123 but using 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-chloro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide. (Found: C, 57.71; H, 5.87; N, 9.29; S, 11.09; Cl, 6.45. C₂₈H₃₅N₄O₃S₂Cl.0.5H₂O requires C, 57.57; H, 6.21; N, 9.59; S, 10.98; Cl, 6.07%).

EXAMPLE 128

Analogously as described for Example 124 but using 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [2-benzothiazol-2-yl-1(RS)-(4-ethyl-piperidine-1-carbonyl)-ethyl]-amide. (Found: C, 61.92; H, 6.89; N, 10.26; S, 12.09. C₂₈H₃₆N₄O₃S₂ requires C, 62.19; H, 6.71; N, 10.36; S, 11.86%).

EXAMPLE 129

Analogously as described for Example 126 but using 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide.

(Found: C, 60.32; H, 6.35; N, 9.94; S, 11.34; F, 3.36. $C_{28}H_{35}N_4O_3S_2F$ requires C, 60.19; H, 6.31; N, 10.03; S, 11.48; F, 3.40%).

EXAMPLE 130

Analogously as described for Example 108 but using N-2-piperidin-4-yl-ethyl-acetamide hydrochloride in place of 1-(2-fluoro-ethyl)-piperazine hydrochloride is prepared N-(2-{1-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl)-acetamide. It has 1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[M+H]^+ = 598.4$.

EXAMPLE 131

Analogously as described for Examples 108 and 109c but using acetic acid 2-piperazin-1-yl-ethyl ester hydrochloride in place of 1-(2-fluoro-ethyl)-piperazine hydrochloride is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-ethyl}-amide hydrochloride. (Found: C, 51.04; H, 6.31; N, 10.38; S, 10.39; Cl, 5.63.

$C_{27}H_{35}N_5O_4S_2 \cdot HCl \cdot H_2O$ requires C, 51.46; H, 6.40; N, 11.11; S, 10.18; Cl, 5.63%).

EXAMPLE 132

Analogously as described for Example 108 but using acetic acid pyrrolidin-2(R)-ylmethyl ester in place of 1-(2-fluoro-ethyl)-piperazine hydrochloride is prepared acetic acid 1-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-pyrrolidin-2(R)-ylmethyl ester. (Found: C, 58.53; H, 6.09; N, 9.45; S, 11.09. $C_{28}H_{34}N_4O_5S_2$ requires C, 58.93; H, 6.00; N, 9.82; S, 11.24%).

EXAMPLE 133

Acetic acid 1-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-pyrrolidin-2(R)-ylmethyl ester is treated as described in Example 109c to give 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [1(S)-benzothiazol-2-yl-methyl-2-(2(R)-hydroxymethyl-pyrrolidin-1-yl)-2-oxo-ethyl]-amide. (Found: C, 58.21; H, 6.30; N, 10.21; S, 11.77. $C_{26}H_{32}N_4O_4S_2 \cdot 0.5H_2O$ requires C, 58.08; H, 6.19; N, 10.42; S, 11.93%).

EXAMPLE 134

Analogously as described for Examples 108 and 109c but using acetic acid 2-piperidin-4-yl-ester hydrochloride in place of 1-(2-fluoro-ethyl)-piperazine hydrochloride is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [2-benzothiazol-2-yl-1(S)-(4-hydroxy-piperidine-1-carbonyl)-ethyl]-amide. (Found: C, 58.94; H, 6.39; N, 9.86; S, 12.78. $C_{26}H_{32}N_4O_4S_2$ requires C, 59.07; H, 6.10; N, 10.60; S, 12.13%).

EXAMPLE 135

Analogously as described for Example 109a-b but using 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride and acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester di-trifluoroacetate salt in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared acetic acid 2-(2-{4-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperazin-1-yl}-ethoxy)-ethyl ester. The 1H -NMR spectrum is consistent with the claimed structure.

EXAMPLE 136

Acetic acid 2-(2-{4-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperazin-1-yl}-ethoxy)-ethyl ester is treated as described in Example 109c to give 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (2-benzothiazol-2-yl-1(S)-{4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazine-1-carbonyl}-ethyl)-amide isolated as its hydrochloride salt as a stable lyophilisate. The ¹H- and ¹³C-NMR spectra are consistent with the claimed structure.

EXAMPLE 137

Analogously as described for Example 135 but using 1-piperidin-4-yl-ethane-1(RS),2-diol hydrochloride in place of acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester di-trifluoroacetate salt is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(1(RS),2-dihydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. Following purification by chromatography on a column of silicagel using ethyl acetate:methanol (99:1, by vol.) as eluant, the product is crystallised from aqueous ethanol. It has m.p. 184-6°C. (Found: C, 58.22; H, 6.32; N, 9.75 S, 11.11. C₂₈H₃₆N₄O₅S₂ requires C, 58.71; H, 6.34; N, 9.78; S, 11.20%).

EXAMPLE 138

Analogously as described for Example 108 but using 3-piperidin-4-yl-propionic acid methyl ester acetate salt in place of 1-(2-fluoro-ethyl)-piperazine hydrochloride is prepared 3-{1-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-propionic acid methyl ester. (Found: C, 56.35; H, 6.09; N, 8.29. C₃₀H₃₈N₄O₅ S₂.2.5H₂O requires C, 55.97; H, 6.73; N, 8.70%).

EXAMPLE 139

Analogously as described for Example 135 but using acetic acid [1,4]diazepan-1-yl-ethyl ester hydrochloride in place of acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester di-trifluoroacetate salt is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-hydroxy-ethyl)-[1,4]diazepane-1-carbonyl]-ethyl}-amide. Found: C, 47.15; H, 6.14; N, 9.75; S, 8.50; $C_{28}H_{37}N_5O_4S_2 \cdot 2HCl \cdot 4H_2O$ requires C, 46.91; H, 6.61; N, 9.77; S, 8.93).

EXAMPLE 140

Analogously as described for Example 135 but using pyrrolidine-2(R)-carboxylic acid methyl ester in place of acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester di-trifluoroacetate salt is prepared 1-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-pyrrolidine-2(R)-carboxylic acid methyl ester. (Found: C, 57.56; H, 5.69; N, 9.96. $C_{27}H_{32}N_4O_5S_2 \cdot 0.5H_2O$ requires C, 57.83; H, 5.88; N, 9.90%).

EXAMPLE 141

1-[3-Benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-pyrrolidine-2(R)-carboxylic acid methyl ester is treated as described in Example 109c to give 1-[3-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-pyrrolidine-2(R)-carboxylic acid. (Found: C, 56.35; H, 5.78; N, 9.61; S, 11.49. $C_{26}H_{30}N_4O_5S_2 \cdot 0.5H_2O$ requires C, 56.61; H, 5.66; N, 10.16; S, 11.62%).

EXAMPLE 142

Analogously as described for Example 108 but using 1-ethyl-piperazine in place of 1-(2-fluoro-ethyl)-piperazine hydrochloride is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [2-benzothiazol-2-yl-1(S)-(4-ethyl-piperazine-1-carbonyl)-ethyl]-amide dihydrochloride. (Found: C, 49.76; H, 6.29; N, 10.88; S, 9.38; Cl, 10.43. $C_{27}H_{35}N_5O_3S_2 \cdot 2HCl \cdot 2H_2O$ requires C, 49.84; H, 6.35; N, 10.76; S, 9.86; Cl, 10.90%).

EXAMPLE 143

Analogously as described for Example 108 but using 4-(2-difluoro-ethyl)-piperazine hydrochloride in place of 1-(2,2-difluoro-ethyl)-piperazine hydrochloride is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2,2-difluoro-ethyl)-piperazine-1-carbonyl]-ethyl}-amide. (Found: C, 52.97; H, 5.63; N, 11.06; S, 10.15. $C_{27}H_{34}N_5S_2O_3F_2 \cdot 2H_2O$ requires C, 52.75; H, 6.23; N, 11.39; S, 10.43%).

EXAMPLE 144

Analogously as described for Example 108 but using 1-piperazine-acetic acid ethyl ester in place of 1-(2-fluoro-ethyl)-piperazine hydrochloride is prepared {4-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperazin-1-yl}-acetic acid ethyl ester. (Found: C, 56.06; H, 5.92; N, 11.03; S, 10.93. $C_{29}H_{37}N_5O_5S_2 \cdot H_2O$ requires C, 56.38; H, 6.36; N, 11.34; S, 10.38%).

EXAMPLE 145

{4-[3-Benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperazin-1-yl}-acetic acid ethyl ester is treated as described in Example 109c to give {4-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperazin-1-yl}-acetic acid. It has 1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[M+H]^+ = 571.7$.

EXAMPLE 146

Analogously as described for Example 135 but using 1-(3-fluoro-propyl)-piperazine hydrochloride in place of acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester di-trifluoroacetate salt is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(3-fluoro-propyl)-piperazine-1-carbonyl]-ethyl}-amide hydrochloride. (Found: C, 51.33; H, 6.34; N, 9.53; S, 8.98; F, 2.43; Cl, 8.47. $C_{28}H_{35}N_5O_3S_2F \cdot HCl \cdot H_2O$ requires C, 51.39; H, 6.08; N, 10.70; S, 9.80; F, 2.90; Cl, 8.13%).

EXAMPLE 147

3-{1-[3-Benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-propionic acid methyl ester is treated as described in Example 109c to give 3-{1-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-propionic acid. It has ¹H- and ¹³C-NMR consistent with the claimed structure. [M+H]⁺ = 584.

EXAMPLE 148

Analogously as described for Example 135 but using piperidin-4-yl-acetic acid methyl ester hydrochloride in place of acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester di-trifluoroacetate salt is prepared {1-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-acetic acid. It has ¹H- and ¹³C-NMR consistent with the claimed structure. [M+H]⁺ = 570.8.

EXAMPLE 149

Analogously as described for Example 129 but using 3(RS),6-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 3(RS),6-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide. The crude product is purified by flash chromatography on silicagel using hexane:ethyl acetate (1:1, by vol) as eluant. It has ¹H-NMR spectrum consistent with the claimed structure. [M+H]⁺ = 558.8.

EXAMPLE 150

Analogously as described for Example 129 but using 3(RS)-methyl-6-methoxy-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 6-methoxy-3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide. The crude product is purified by flash chromatography on silicagel using hexane:ethyl acetate (1:1, by vol.) as eluant. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 574.

EXAMPLE 151

6-Methoxy-3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide (205mg) is dissolved in dry dichloromethane (2ml) and cooled to -78°C. Boron tribromide (268 mg) in dry dichloromethane (1ml) is added and the mixture is stirred with exclusion of moisture for 1 hour at 20°C. Methanol (1ml) is added and the mixture is evaporated to dryness in vacuo. The residue is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (25:1, by vol.) as eluant to give 6-hydroxy-3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-bromo-ethyl)-piperidine-1-carbonyl]-ethyl}-amide as a colourless oil. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 621, 622.8.

EXAMPLE 152

a) (8-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid (1g) and triethylamine (0.26ml) are dissolved in DMF (25ml), the solution is cooled to 0°C and ethyl chloroformate (0.18ml) is added. The mixture is stirred and allowed to warm to room temperature and stirred for a further 15 minutes. The mixture is diluted with ethyl acetate (200ml) and extracted with water (3x100ml). The organic phase is dried (MgSO₄) and evaporated to dryness to give crude 6-(2-ethoxycarbonyl-acetyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a white solid.

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b) Crude 6-(2-ethoxycarbonyl-acetyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (1.21g) is dissolved in ethanol (6ml) at 0°C and sodium borohydride (120mg) is added. The mixture is stirred for 20 minutes, water (0.1ml) is added and the mixture is diluted with ethyl acetate (20ml) and washed with saturated aqueous sodium bicarbonate (3x10ml). The organic phase is dried (MgSO₄) and evaporated. The residue is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (3:1, by vol.) as eluant to give 6-hydroxymethyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide as a white solid. It has 1H and 13C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 590.

EXAMPLE 153

Analogously as described for Example 135 but using 1-fluoro-3-piperazin-1-yl-propan-2(RS)-ol trifluoroacetic acid salt in place of acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester di-trifluoroacetate salt is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(3-fluoro-2(RS)-hydroxy-propyl)-piperazine-1-carbonyl]-ethyl}-amide hydrochloride as a freeze-dried solid. It has 1H-NMR spectrum consistent with the claimed structure. [M+H]⁺ = 590.2.

EXAMPLE 154

Analogously as described for Example 135 but using 2,2,2-trifluoro-1(RS)-piperidin-4-yl-ethanol hydrochloride in place of acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester di-trifluoroacetate salt is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {(1S)-benzothiazol-2-ylmethyl-2-[4-(2,2,2-trifluoro-1(RS)-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. It is purified by flash chromatography on a column of silicagel using dichloromethane:ethyl acetate (4:1, by vol.) as eluant. It has 1H-NMR spectrum consistent with the claimed structure. [M+H]⁺ = 611.

EXAMPLE 155

6-Hydroxymethyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide (300mg) and 4-methylmorpholine N-oxide (90mg) are suspended, with molecular sieves (4 Angstroms) (250mg) in dry dichloromethane (4ml) and tetrapropylammonium perruthenate (9mg) is added. The mixture is stirred at 20°C for 15 minutes, filtered and the filtrate applied to a column of silicagel which is eluted with ethyl acetate:hexane (2:1, by vol.) to give 6-formyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide as a white solid. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 586.4.

EXAMPLE 156

6-Hydroxymethyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide (54mg) and Huenig Base (0.024ml) are dissolved in dry dichloromethane (1ml) and methoxyethoxymethyl chloride (0.016ml) is added. The mixture is stirred at 20°C for 6 hours. Solvent is removed by rotary evaporation and the residue is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (2:1, by vol.) as eluant to give 6-(2-methoxy-ethoxymethoxymethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide as a colourless oil. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 677.2.

EXAMPLE 157

a) 6-Formyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide (200mg) is dissolved in dry dichloromethane (3ml) and carboethoxymethylene triphenylphosphorane (236mg) is added. The mixture is stirred at 20°C for 24 hours and applied to a column of silicagel which is eluted with ethyl acetate:hexane (1:1, by vol.) to give 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-acrylic acid ethyl ester as a pale yellow oil.

b) 3-(8-{2-Benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-acrylic acid ethyl ester (21.5mg) is dissolved in methanol (2ml) and aqueous sodium hydroxide (M, 0.5ml) is added. The mixture is stirred at 20°C for 18 hours and solvents are removed by rotary evaporation. The residue is triturated with aqueous hydrochloric acid (2M) and the solid recovered by filtration. It is dissolved in ethyl acetate (5ml) and the solution is washed with water (5ml), dried (MgSO₄) and evaporated. The residue is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (20:1, by vol.) as eluant to give 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-acrylic acid as a white solid. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 628.6.

EXAMPLE 158

a) Analogously as described for Example 108b but using 2(S)-tert.-butoxycarbonyl-amino-3-thienyl propionic acid in place of 2(S)-benzyloxycarbonyl-amino-3-benzothiazol-2-yl propionic acid and acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride in place of 1-(2-fluoro-ethyl)-piperazine is prepared 2(S)-tert.-butoxycarbonylamino-3-thien-2-yl-1-{4-(2-acetoxy-ethyl)-piperidin-1-yl}-propan-1-one.

b) Analogously as described for Example 111e but using 2(S)-tert.-butoxycarbonyl-amino-3-thien-2-yl-1-{4-(2-acetoxy-ethyl)-piperidin-1-yl}-propan-1-one in place of acetic acid 2-{1-[2(S)-tert.-butoxycarbonylamino-3-(4-chloromethyl-thiazol-2-yl)-propionyl]-piperidin-4-yl}-ethyl ester is prepared 2(S)-amino-3-thien-2-yl-1-{4-(2-acetoxy-ethyl)-piperidin-1-yl}-propan-1-one hydrochloride.

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c) Analogously as described for Example 108d but using 2(S)-amino-3-thien-2-yl-1-{4-(2-acetoxy-ethyl)-piperidin-1-yl}-propan-1-one hydrochloride in place of 2(S)-amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperazin-1-yl]-propan-1-one hydrobromide is prepared acetic acid 2-{1-[2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-3-thiophen-2-yl-propionyl]-piperidin-4-yl}-ethyl ester. It is purified by flash chromatography on a column of silicagel using ether:hexane (3:1, by vol.) as eluant. (Found: C, 58.64; H, 7.06; N, 7.61; S, 11.96. $C_{27}H_{37}N_3O_5S_2$ requires C, 59.21; H, 6.81; N, 7.67; S, 11.71%).

EXAMPLE 159

Analogously as described for Example 135 but using trans-4-(2-acetoxy-ethyl)-piperidine-2-carboxylic acid ethyl ester in place of acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester di-trifluoroacetate salt is prepared trans-4-(2-acetoxy-ethyl)-1-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidine-2-carboxylic acid ethyl ester. It has 1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[M+H]^+ = 671.25$.

EXAMPLE 160

Analogously as described for Example 109c but using trans-4-(2-acetoxy-ethyl)-1-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidine-2-carboxylic acid ethyl ester in place of acetic acid 2-{1-[3-benzothiazol-2-yl-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester is prepared 1-[3-benzothiazol-2-yl-2(S)-(3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-trans-4-(2-hydroxy-ethyl)-piperidine-2-carboxylic acid. It is converted to its sodium salt by addition of a calculated amount of aqueous sodium hydroxide solution to a strong solution of the acid in ethanol. Trituration with ether gives the sodium salt as a solid. $[M+H]^+ = 601.21$.

EXAMPLE 161

Analogously as described for Example 108 but starting from 2(R)-benzyloxycarbonylamino-3-benzothiazol-2-yl-propionic acid benzyl ester in place of 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-propionic acid benzyl ester is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(R)-[4-(2-fluoro-ethyl)-piperazine-1-carbonyl]-ethyl}-amide. It is purified by flash chromatography on a column of silicagel using ethyl acetate:ethanol (9:1, by vol.) as eluant. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 558.8.

EXAMPLE 162

a) 3-Amino-4-hydroxy-pyridine (3.66g) is dissolved in pyridine (112ml) at 20°C and DMAP (220mg) is added followed by 2(S)-benzyloxycarbonylamino-3-chlorocarbonyl-propionic acid benzyl ester (7.5g). The mixture is stirred for 5 hours and solvents are removed by rotary evaporation. The residue is dissolved in ethyl acetate (200ml) and extracted with portions (100ml) of water which are back-extracted (2x) with ethyl acetate (200ml). The combined organic phases are washed with brine (100ml), dried (MgSO₄) and solvent is removed by rotary evaporation. The residue is purified by chromatography on a column of silicagel using methanol:ethyl acetate (1:49, then 1:9, by vol.) as eluant to give 2(S)-benzyloxycarbonylamino-N-(4-hydroxypyridin-3-yl)-succinamic acid benzyl ester as a white solid.

b) 2(S)-Benzyloxycarbonylamino-N-(4-hydroxypyridin-3-yl)-succinamic acid benzyl ester (1.0g) and Lawesson's Reagent (1.6g) are dissolved in toluene (48ml) and the mixture is heated at 90°C for 2.5 hours, then cooled to room temperature and poured into a mixture of water and ethyl acetate (200 ml of each). The aqueous fraction is extracted with ethyl acetate (2x100ml) and the combined organic extracts are washed with brine (2x200ml), dried (MgSO₄) and the solvent evaporated to give a brown oil which is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (3:1, by vol.) as eluant to afford pure 2(S)-benzyloxycarbonylamino-3-thiazolo[4,5-c]pyridin-2-yl-propionic acid benzyl ester.

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c) Analogously as described in Example 108 but using 2(S)-benzyloxycarbonylamino-3-thiazolo[4,5-c]pyridin-2-yl-propionic acid benzyl ester in place of 2(S)-benzyloxycarbonyl-3-benzothiazol-2-yl-propionic acid benzyl ester and 4-(2-fluoro-ethyl)-piperidine in place of 1-(2-fluoro-ethyl)-piperazine is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-thiazolo[4,5-c]pyridin-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide, which is dissolved in ethanol (1ml) and converted to the hydrochloride salt by addition of hydrogen chloride in ether (2ml) from which mixture the hydrochloride salt is obtained as a white solid which is collected by filtration, washed with ether and lyophilised from aqueous solution. It has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 560.06$.

EXAMPLE 163

Analogously as described for Example 162 but using 5-amino-pyrimidin-4-ol in place of 3-amino-4-hydroxy-pyridine is prepared 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-thiazolo[5,4-d]pyrimidin-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. It has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 561$.

EXAMPLE 164

a) Analogously as described for Example 129 but using 6-[2-(tert.-butyl-diphenyl-silanyloxy)-ethyl]-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 6-[2-(tert.-butyl-diphenyl-silanyloxy)-ethyl]-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-fluoro-ethyl-piperidin-1-yl]-2-oxo-ethyl}-amide. It is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:1, by vol.) as eluant.

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b) 6-[2-(tert.-Butyl-diphenyl-silanyloxy)-ethyl]-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzo-thiazol-2-ylmethyl-2-[4-fluoro-ethyl-piperidin-1-yl]-2-oxo-ethyl}-amide (245mg) dissolved in dry THF (10ml) and TBAF (1M in THF, 0.575ml) are mixed and stirred for 70 hours at 20°C. The solution is pre-absorbed onto silicagel and purified by column chromatography on a column of silicagel using ethyl acetate:hexane (2:1, by vol.) as eluant. 6-(2-Hydroxy-ethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-fluoro-ethyl-piperidin-1-yl]-2-oxo-ethyl}-amide is obtained as a stable solid after freeze-drying. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 603.

EXAMPLE 165

3-(8-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-acrylic acid ethyl ester (188mg) is dissolved in dry methanol (2ml) and copper(I)chloride (56mg) added. Sodium borohydride (108mg) is added to the cooled solution at 0°C over 1 hour. The mixture is filtered through a plug of cotton wool and the filtrate diluted with ether (10ml) and washed with portions (5ml) of aqueous hydrochloric acid (2M), brine and saturated aqueous sodium bicarbonate, dried (MgSO₄) and the solvents evaporated to give a residue which is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (3:2, by vol.) as eluant. 3-(8-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester is obtained as a colourless oil. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 658.4.

EXAMPLE 166**Method 1**

3-(8-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (93mg) is dissolved in methanol (6ml) and aqueous sodium hydroxide (M, 2ml) is added. The mixture is stirred at 20°C for 18 hours and aqueous hydrochloric acid (2M, 1ml) is added. Ethyl acetate (20ml) is added, the organic phase is washed with water (10ml) and dried (MgSO₄) and evaporated to give 3-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid as white crystals after recrystallisation from acetonitrile. It has 1H- and 13C-NMR spectra consistent with the claimed structure, m.p. 224°C. [M+H]⁺ = 630.50. (Found: C, 58.95; H, 6.05; N, 8.86; S, 10.10; F = 3.13. C₃₁H₃₉N₄O₅S₂F requires C, 59.03; H, 6.23; N, 8.88; S, 10.17; F = 3.01%).

Method 2

Analogously as described for Example 110 but using 3-(8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester in place of 8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester is prepared 3-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid which is crystallised from acetonitrile and is identical to the material prepared by Method 1 above.

EXAMPLE 167

Analogously as described in Example 152 but using 3-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid in place of (8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid is prepared 3,3-dimethyl-6-(3-hydroxy-propyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a white solid. It has ¹H and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 617.

EXAMPLE 168

Analogously as described for Example 156 but using methoxymethyl chloride in place of methoxyethoxymethyl chloride and purifying by flash chromatography on a column of silicagel using ethyl acetate:hexane (2:3, by vol.) is obtained 3,3-dimethyl-6-methoxymethoxymethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a colourless oil. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 632.6.

EXAMPLE 169

Analogously as described for Example 120 but using N-tert.-butoxycarbonyl-(S)-tryptophan in place of 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-propionic acid and 3-methyl-quinoline-8-sulfonyl chloride coupling followed by catalytic hydrogenation as described for Example 12b is prepared acetic acid 2-{1-[3-(1H-indol-3-yl)-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester. (Found: C, 63.37; H, 6.83; N, 9.62; S, 5.69. C₃₀H₃₈N₄O₅S requires C, 63.58; H, 6.76; N, 9.89; S, 5.66%).

EXAMPLE 170

Analogously as described for Example 169 but using quinoline-8-sulfonyl chloride in place of 3-methyl-quinoline-8-sulfonyl chloride is prepared acetic acid 2-{1-[3-(1H-indol-3-yl)-2(S)-(1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester. It is obtained as a solid by trituration with hexane. After drying at high vacuum for 72 hours, the presence of hexane in the product is demonstrated by ¹³C-NMR spectroscopy. (Found: C, 64.04; H, 7.20; N, 9.55; S, 5.25.

C₂₉H₃₆N₄O₅S.0.4C₆H₁₄ requires C, 64.23; H, 7.14; N, 9.54; S, 5.46%).

EXAMPLE 171

Analogously as described for Example 109c but using acetic acid 2-{1-[3-(1H-indol-3-yl)-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester in place of acetic acid 2-{1-[3-benzothiazol-2-yl-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-[1H-indol-3-ylmethyl]-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a freeze-dried solid. (Found: C, 63.03; H, 6.76; N, 10.24; S, 5.69.

C₂₈H₃₆N₄O₄S.0.5H₂O requires C, 63.01; H, 6.99; N, 10.50; S, 6.01%).

EXAMPLE 172

Analogously as described for Example 171 but using acetic acid 2-{1-[3-(1H-indol-3-yl)-2(S)-(1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester in place of acetic acid 2-{1-[3-(1H-indol-3-yl)-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester is prepared 1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-[1H-indol-3-ylmethyl]-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a freeze-dried solid. (Found: C, 61.78; H, 6.70; N, 10.18; S, 5.84. C₂₇H₃₄N₄O₄S.H₂O requires C, 61.34; H, 6.86; N, 10.60; S, 6.07%).

EXAMPLE 173

Analogously as described for Example 169 but using N-tert.-butoxycarbonyl-(R)-tryptophan in place of N-tert.-butoxycarbonyl-(S)-tryptophan is prepared acetic acid 2-{1-[3-(1H-indol-3-yl)-2(R)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester. (Found: C, 62.99; H, 6.59; N, 9.54; S, 5.66. $C_{30}H_{38}N_4O_5S$ requires C, 62.59; H, 6.83; N, 9.73; S, 5.57%).

EXAMPLE 174

Analogously as described for Example 170 but using N-tert.-butoxycarbonyl-(R)-tryptophan in place of N-tert.-butoxycarbonyl-(S)-tryptophan is prepared acetic acid 2-{1-[3-(1H-indol-3-yl)-2(R)-(1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester. (Found: C, 59.94; H, 6.24; N, 9.39; S, 4.89. $C_{29}H_{36}N_4O_5S \cdot 1.5H_2O$ requires C, 60.08; H, 6.78; N, 9.67; S, 5.53%).

EXAMPLE 175

Analogously as described for Example 171 but using acetic acid 2-{1-[3-(1H-indol-3-yl)-2(R)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester in place of acetic acid 2-{1-[3-(1H-indol-3-yl)-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(R)-[1H-indol-3-ylmethyl]-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a freeze-dried solid. (Found: C, 61.27; H, 7.07; N, 9.74; S, 5.93. $C_{28}H_{36}N_4O_4S \cdot 1.5H_2O$ requires C, 60.96; H, 7.13; N, 10.16; S, 5.81%).

EXAMPLE 176

Analogously as described for Example 172 but using acetic acid 2-{1-[3-(1H-indol-3-yl)-2(R)-(1,2,3,4-tetrahydro-quinoline-8-sulfonyl-amino)-propionyl]-piperidin-4-yl}-ethyl ester in place of acetic acid 2-{1-[3-(1H-indol-3-yl)-2(S)-(1,2,3,4-tetrahydro-quinoline-8-sulfonyl-amino)-propionyl]-piperidin-4-yl}-ethyl ester is prepared 1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(R)-[1H-indol-3-ylmethyl]-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a freeze-dried solid. (Found: C, 62.26; H, 6.72; N, 10.27; S, 6.02. $C_{27}H_{34}N_4O_4S \cdot 0.5H_2O$ requires C, 62.40; H, 6.79; N, 10.78; S, 6.17%).

EXAMPLE 177

Analogously as described for Examples 169 and 118b but using 6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3-methyl-quinoline-8-sulfonyl chloride is prepared acetic acid 2-{1-[3-(1H-indol-3-yl)-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino]-propionyl]-piperidin-4-yl}-ethyl ester as a freeze-dried solid. (Found: C, 62.80; H, 7.00; N, 9.02. $C_{31}H_{40}N_4O_5S \cdot H_2O$ requires C, 62.18; H, 7.07; N, 9.36%).

EXAMPLE 178

Analogously as described for Example 169 but using N-methyl-N-tert.-butoxycarbonyl-(S)-tryptophan in place of N-tert.-butoxycarbonyl-(S)-tryptophan is prepared acetic acid 2-{1-[3-(1H-indol-3-yl)-2(S)-[methyl-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl)-amino]-propionyl]-piperidin-4-yl}-ethyl ester. (Found: C, 63.88; H, 6.98; N, 9.62. $C_{31}H_{40}N_4O_5S$ requires C, 64.11; H, 6.94; N, 9.65%).

EXAMPLE 179

Analogously as described for Example 169 but using 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3-methyl-quinoline-8-sulfonyl chloride and N-(tert.-butoxycarbonyl-5-hydroxy-(S)-tryptophan in place of N-(tert.-butoxycarbonyl-(S)-tryptophan is prepared acetic acid 2-{1-[3-(5-hydroxy-1H-indol-3-yl)-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester. It has ^{13}C -NMR spectrum consistent with the claimed structure. $[M+H]^+ = 583$.

EXAMPLE 180

a) Analogously as described for Example 169 but using N-tert.-butoxycarbonyl-2,5-diiodo-(S)-histidine in place of N-tert.-butoxycarbonyl-(S)-tryptophan is prepared acetic acid 2-{1-[3-(2,5-diiodo-1 H-imidazol-4-yl)-2(S)-(3-methyl-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester.

b) Acetic acid 2-{1-[3-(2,5-diiodo-1H-imidazol-4-yl)-2(S)-(3-methyl-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester (1.27g) is dissolved in a mixture of methanol (40ml) and acetic acid (0.4ml) and hydrogenated in the presence of 10% (by weight) palladium on charcoal (0.2g) for 72 hours at 20°C. The catalyst is removed by filtration and the filtrate dried by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using chloroform:methanol:acetic acid (4:1:1, by vol.) as eluant. The product is dissolved in aqueous methanol (1:1, by vol., 4ml) and passed through a column (1ml) of Dowex 1 (acetate form) resin. The eluate is partially evaporated and then freeze-dried to give acetic acid 2-{1-[3-(1H-imidazol-4-yl)-2(S)-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester as a white solid. (Found: C, 52.46; H, 5.98; N, 12.22, S, 5.65. $C_{25}H_{35}N_5O_5S \cdot 3H_2O$ requires C, 52.52; H, 7.23; N, 12.25; S, 5.61%).

EXAMPLE 181

3,3-Dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (279mg) and Lawesson's Reagent (101mg) are dissolved in dry toluene (5ml) and the mixture is kept at 80°C for 16 hours. The mixture is dried by rotary evaporation and the residue purified by flash chromatography on a column of silicagel using dichloromethane:ethyl acetate (19:1, by vol.) as eluant to give 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbothioyl]-ethyl}-amide. (Found: C, 58.41; H, 6.24; N, 9.44; S, 15.42. $C_{28}H_{35}N_4O_2S_3F$ requires C, 58.51; H, 6.14; N, 9.75; S, 16.74%).

EXAMPLE 182

Analogously as described for Example 169 but using [2(RS)-tert.-butoxycarbonyl-amino]-benzo[.b.]thiophen-2-yl-acetic acid in place of N-tert.-butoxycarbonyl-(S)-tryptophan is prepared acetic acid 2-{1(RS)-[2-benzo[.b.]thiophen-2-yl-2-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-acetyl]-piperidin-4-yl}-ethyl ester. (Found: C, 61.26; H, 6.26; N, 7.21; S, 10.98. $C_{29}H_{35}N_3O_5S_2$ requires C, 61.13; H, 6.19; N, 7.38; S, 11.26%).

EXAMPLE 183

Analogously as described for Example 109c but using acetic acid 2-{1(RS)-[2-benzo[.b.]thiophen-2-yl-2-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-acetyl]-piperidin-4-yl}-ethyl ester in place of acetic acid 2-{1-[3-benzothiazol-2-yl-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(RS)-benzo[.b.]thiophen-2-yl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. (Found: C, 61.37; H, 6.32; N, 7.66. $C_{27}H_{33}N_3O_4S_2$ requires C, 61.45; H, 6.30; N, 7.96%).

EXAMPLE 184

Analogously as described for Example 169 but using 3-piperidin-4-yl-propionic acid methyl ester acetate salt in place of acetic acid 2-piperidinyl-ethyl ester hydrochloride and [2(RS)-tert.-butoxy-carbonyl-amino]-benzo[.b.]thiophen-2-yl-acetic acid in place of N-tert.-butoxycarbonyl-(S)-tryptophan is prepared 3-{1(RS)-[2-benzo[.b.]thiophen-2-yl-2-(3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-acetyl]-piperidin-4-yl}-propionic acid methyl ester. (Found : C, 61.13; H, 6.10; N, 7.17; S, 11.11. $C_{29}H_{35}N_3O_5S_2$ requires C, 61.13; H, 6.19; N, 7.38; S, 11.26%).

EXAMPLE 185

Analogously as described for Example 182 but using N-(2-piperidin-4-yl-ethyl)-methanesulfonamide in place of acetic acid 2-piperidin-4-yl-ethyl ester hydrochloride is prepared 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(RS)-benzo[.b.]thiophen-2-yl-2-[4-(2-methylsulfonyl-amino-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. (Found: C, 55.81; H, 6.14; N, 8.74; S, 15.35. $C_{28}H_{36}N_4O_5S_3$ requires C, 55.60; H, 6.00; N, 9.26; S, 15.91%).

EXAMPLE 186

Analogously as described for Example 182 but starting from 3-(1-methyl-1-phenyl-ethyl)-benzenesulfonyl chloride in place of 3-methyl-quinoline-8-sulfonyl chloride and acetic acid [2(RS)-tert.-butoxycarbonyl-amino]-benzo[.b.]thiophen-3-yl-acetic acid in place of [2(RS)-tert.-butoxycarbonyl-amino]-benzo[.b.]thiophen-2-yl-acetic acid is prepared acetic acid 2(RS)-(1-{2-benzo[.b.]thiophen-3-yl-2-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-acetyl}-piperidin-4-yl)-ethyl ester. (Found: C, 65.78; H, 6.06; N, 4.54. $C_{34}H_{38}N_2O_5S_2$ requires C, 65.99; H, 6.19; N, 4.53%).

EXAMPLE 187

Analogously as described for Example 109c but using acetic acid 2(RS)-(1-{2-benzo[.b.]thiophen-3-yl-2-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-acetyl}-piperidin-4-yl)-ethyl ester in place of acetic acid 2-{1-[3-benzothiazol-2-yl-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl)-ethyl ester is prepared 3-(1-methyl-1-phenyl-ethyl)-benzene sulfonic acid {1(RS)-benzo[.b.]thiophen-3-yl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. (Found: C, 66.81; H, 6.54; N, 4.89. $C_{32}H_{36}N_2O_4S_2$ requires C, 66.81; H, 6.29; N, 4.86%).

EXAMPLE 188

Analogously as described for Example 186 but using [2(RS)-tert.-butoxy-carbonyl-amino]-benzo[.b.]thiophen-2-ylmethyl-acetic acid in place of [2(RS)-tert.-butoxy-carbonyl-amino]-benzo[.b.]thiophen-2-yl-acetic acid is prepared acetic acid 2-(1-{2(RS)-benzo[.b.]thiophen-2-ylmethyl-2-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-acetyl}-piperidin-4-yl)-ethyl ester. (Found: C, 66.40; H, 6.32; N, 4.57; S, 10.24. $C_{35}H_{40}N_2O_5S_2$ requires C, 66.46; H, 6.33; N, 4.43; S, 10.13%).

EXAMPLE 189

Analogously as described for Example 186 but using [2(RS)-tert.-butoxycarbonyl-amino]-benzo[.b.]thiophen-3-ylmethyl-acetic acid in place of [2(RS)-tert.-butoxycarbonyl-amino]-benzo[.b.]thiophen-3-yl-acetic acid is prepared acetic acid 2-(1-{2(RS)-benzo[.b.]thiophen-3-ylmethyl-2-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-acetyl}-piperidin-4-yl)-ethyl ester. (Found: C, 66.64; H, 6.14; N, 4.65; S, 10.06. $C_{35}H_{40}N_2O_5S_2$ requires C, 66.43; H, 6.37; N, 4.43; S, 10.13%).

EXAMPLE 190

Analogously as described for Example 187 but using acetic acid 2-(1-{2(RS)-benzo[.b.]thiophen-3-ylmethyl-2-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-acetyl}-piperidin-4-yl)-ethyl ester in place of acetic acid 2(RS)-(1-{2-benzo[.b.]thiophen-3-yl-2-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-acetyl}-piperidin-4-yl)-ethyl ester is prepared 3-(1-methyl-1-phenyl-ethyl)-benzene sulfonic acid {1(RS)-benzo[.b.]thiophen-3-ylmethyl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. (Found: C, 67.11; H, 6.35; N, 4.88; S, 10.60. $C_{33}H_{38}N_2O_4S_2$ requires C, 67.09; H, 6.48; N, 4.74; S, 10.85%).

EXAMPLE 191

Analogously as described for Example 182 but using 3-(1-methyl-1-phenyl-ethyl)-benzene sulfonyl chloride in place of 3-methyl-quinoline-8-sulfonyl chloride is prepared acetic acid 2(RS)-(1-{2-benzo[b.]thiophen-2-yl-2-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-acetyl}-piperidin-4-yl)-ethyl ester. (Found: C, 65.84; H, 6.22; N, 4.53. $C_{34}H_{38}N_2O_5S_2$ requires C, 65.99; H, 6.19; N, 4.53%).

EXAMPLE 192

Analogously as described for Example 109c but using acetic acid 2(RS)-(1-{2-benzo[b.]thiophen-2-yl-2-[3-(1-methyl-1-phenyl-ethyl)-benzenesulfonylamino]-acetyl}-piperidin-4-yl)-ethyl ester in place of acetic acid 2-{1-[3-benzothiazol-2-yl-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester is prepared 3-(1-methyl-1-phenyl-ethyl)-benzene sulfonic acid {1(RS)-benzo[b.]thiophen-2-yl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. (Found: C, 66.34; H, 6.32; N, 4.62; S, 11.07. $C_{32}H_{36}N_2O_4S_2$ requires C, 66.64; H, 6.29; N, 4.86; S, 11.12%).

EXAMPLE 193

Analogously as described for Example 120 but using 3-(1-methyl-1-phenyl-ethyl)-benzene sulfonyl chloride in place of 3(RS)-methyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared acetic acid 2-{1-[3-benzthiazol-2-yl-2(S)-(3-(1-methyl-1-phenyl-ethyl)-benzene-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester. (Found: C, 64.44; H, 6.32; N, 6.41, S, 9.61. $C_{34}H_{39}N_3O_5S_2$ requires C, 64.43; H, 6.20; N, 6.63; S, 10.12%).

EXAMPLE 194

Analogously as described for Example 109c but using acetic acid 2-{1-[3-benzthiazol-2-yl-2(S)-(3-(1-methyl-1-phenyl-ethyl)-benzene-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester in place of acetic acid 2-{1-[3-benzothiazol-2-yl-2(S)-(6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonylamino)-propionyl]-piperidin-4-yl}-ethyl ester is prepared N-{2-benzothiazol-2-yl-1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-ethyl}-3-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide. (Found: C, 63.05; H, 6.30; N, 6.47; S, 9.98. $C_{32}H_{37}N_3O_4S_2 \cdot H_2O$ requires C, 63.03; H, 6.45; N, 6.89; S, 10.52%).

EXAMPLE 195

Analogously as described for Example 110 but using 8-chlorosulfonyl-3,3-diethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester in place of 8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester is prepared 8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-diethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid as a white solid. It has 1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[M+H]^+ = 631.4$.

EXAMPLE 196

6-(2-Hydroxy-ethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (50mg) is dissolved in a mixture of dichloromethane (1ml), acetonitrile (1ml) and water (1.5ml) and sodium periodate (73mg) and ruthenium dichloride hydrate (0.4mg) are added. The mixture is stirred at 20°C for 2 hours and then extracted with dichloromethane (2x10ml). The combined extracts are dried ($MgSO_4$) and evaporated to give a residue which is purified by flash chromatography on a column of silicagel using ethyl acetate as eluant to give 6-carboxymethyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-yl-methyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a white solid after freeze-drying. It has 1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[M+H]^+ = 617.4$.

EXAMPLE 197

Analogously as described for Example 110 but using 3-(8-chlorosulfonyl-3,3-diethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester in place of 8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester is prepared 3-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-3,3-diethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid as a white solid. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 659.8.

EXAMPLE 198

Analogously as described for Example 152 but starting from (8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-3,3-diethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid is prepared 3,3-diethyl-6-hydroxymethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a white solid. The crude product is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (2:1, by vol.) as eluant. It has ¹H and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 617.5.

EXAMPLE 199

a) Analogously as described for Example 155 but starting from 3,3-diethyl-6-hydroxymethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide is prepared 3,3-diethyl-6-formyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a white foam. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 615.5.

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b) 3,3-Diethyl-6-formyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (250mg) is dissolved in methanol (15ml, dried over 4 Angstrom molecular sieves) and dry sodium acetate (200mg) is added to the stirred solution. Hydroxylamine hydrochloride (141mg) is added and the solution is stirred for 30 minutes at 20°C. The mixture is diluted with brine (50ml) and extracted with portions (2x25ml) of dichloromethane. The combined extracts are dried (MgSO₄) and the solvent removed by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (2:1, by vol.) as eluant to give 3,3-diethyl-6-(hydroxyimino-methyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide as a white foam. It has 1H- and 13C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 630.6.

EXAMPLE 200

a) 3,3-Diethyl-6-(hydroxyimino-methyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide (183mg) is dissolved in dry dichloromethane (5ml), carbonyldiimidazole (141mg) and pyridine (47μl) are added and the mixture is heated at reflux for 18 hours. The mixture is diluted with dichloromethane (15ml), washed with portions (3x10ml) of aqueous hydrochloric acid (0.1M) and the organic phase evaporated to dryness. The residue is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (2:1, by vol.) as eluant to give 3,3-diethyl-6-(cyano-methyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide as a colourless oil. It has 1H- and 13C-NMR spectra consistent with the claimed structure.

b) 3,3-Diethyl-6-(cyano-methyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide (103mg) is dissolved in xylene (6ml) and tributyl tin azide (112mg) is added. The mixture is stirred at 130°C for 24 hours and the solvent is removed by rotary evaporation. The residue is dissolved in aqueous sodium hydroxide solution (2M, 5ml) with addition of sufficient methanol to effect solution and extracted with portions (3x5ml) of ether:hexane (1:1, by vol.).

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The aqueous phase is acidified (2M aqueous hydrochloric acid) and extracted with portions (3x5ml) of ethyl acetate. The combined extracts are dried (MgSO_4) and dried by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (20:1, by vol.) as eluant to give 3,3-dimethyl-6-(1H-tetrazol-5-ylmethyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {(2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl)-amide as a white foam. It has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 655.6$.

EXAMPLE 201

a) 3,3-Dimethyl-6-formyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (2.356g) is dissolved in dry dichloromethane (50ml) and cyanomethylene triphenylphosphorane (3.618g) is added. The mixture is stirred for 30 hours at 20°C under an atmosphere of nitrogen and the solution is applied directly onto a column of silicagel. The product is recovered by flash chromatography using hexane:ethyl acetate (1:1, by vol.) as eluant to give a mixture of the cis and trans isomers of 6-cyano-vinyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide as a colourless foam.

b) 6-Cyano-vinyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide (500mg) and copper(I)chloride (162mg) are dissolved in dry methanol (15ml) and sodium borohydride (310mg) is added during 30 minutes with stirring. The mixture is filtered (Celite) and the filtrate is diluted with ether (25ml) and extracted with portions (2x15ml) of aqueous hydrochloric acid (2M). The organic phase is dried (MgSO_4) and the solvents removed by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (2:1, by vol.) as eluant to give 3,3-dimethyl-6-(2-cyano-ethyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide as a white foam.

c) Analogously as described for Example 200 but starting from 3,3-dimethyl-6-(2-cyano-ethyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide in place of 3,3-dimethyl-6-cyano-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide is prepared 3,3-dimethyl-6-[2-(1H-tetrazol-5-yl)-ethyl]-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. $[M+H]^+ = 655.5$.

EXAMPLE 202

a) A solution of dimethyl sulfoxide (0.2ml) in dry dichloromethane (3ml) is cooled to -50°C and phosgene (124μl) is added. The mixture is stirred for 2 minutes and 6-(2-hydroxy-ethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (430mg) in dry dichloromethane (2ml) is added. The mixture is stirred for 15 minutes, triethylamine (497μl) is added and the mixture is stirred for 5 minutes and then allowed to rise to room temperature. Dichloromethane (10ml) is added, the solution is washed with portions (10ml) of water and aqueous hydrochloric acid (2M), dried ($MgSO_4$) and the solvents removed by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (20:1, by vol.) as eluant to give 3,3-dimethyl-6-formylmethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as an orange oil which is sufficiently pure for further use.

b) Analogously as described for Examples 199b and 200a-b but starting from crude 3,3-dimethyl-6-formylmethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide in place of 3,3-dimethyl-6-formyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide is prepared 3,3-dimethyl-6-(1H-tetrazol-5-ylmethyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. $[M+H]^+ = 641.4$.

EXAMPLE 203

- a) Analogously as described for Example 157 but starting from 3,3-dimethyl-6-formylmethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide in place of 3,3-dimethyl-6-formyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide is prepared 4-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-but-2-enoic acid ethyl ester. It is purified by flash chromatography on a column of silicagel eluted with ethyl acetate:hexane (1:1, by vol.) to give a white foam.
- b) Analogously as described for Example 165 but starting from 4-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-but-2-enoic acid ethyl ester in place of 3-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-acrylic acid ethyl ester is prepared 4-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-butanoic acid ethyl ester.
- c) Analogously as described for Example 166 but starting from 4-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-butanoic acid ethyl ester in place of 3-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propanoic acid ethyl ester is prepared 4-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-butanoic acid. The crude product is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (9:1, by vol.) as eluant. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 645.3.

EXAMPLE 204

Analogously as described for Example 108 but using 4-(2-fluoro-ethyl)-piperidine hydrochloride in place of 1-(2-fluoro-ethyl)-piperazine hydrochloride and 3,3-dimethyl-6-fluoro-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 3,3-dimethyl-6-fluoro-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid [2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl]-amide. After purification by flash chromatography on a column of silicagel using ethyl acetate:dichloromethane (1:9, by vol.) as eluant and evaporation of the solvent, it is obtained as a white foam. It has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 577.9$.

EXAMPLE 205

Analogously as described for Example 129 but using 3-(8-chlorosulfonyl-3(RS)-ethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-ethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid. The ester is saponified as described in Example 109c and the final compound is extracted after acidification (aqueous HCl) of the saponification mixture with ethyl acetate, and after water washing of the extracted solution and drying (MgSO_4) is recovered on evaporation of the solvent as a white foam. $[\text{M}+\text{H}] = 631.2$. The ^{13}C - and ^1H -NMR spectra are consistent with the claimed structure.

EXAMPLE 206

Analogously as described for Example 205 but using 3-(8-chlorosulfonyl-3(RS)-propyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester is prepared 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-propyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid. The compound precipitates on acidification (aqueous HCl) of the saponification mixture and, after solution of the precipitate in ethyl acetate, water washing of the solution and drying (MgSO_4) is recovered on evaporation of the solvent as a white foam. $[\text{M}+\text{H}] = 645.2$. The ^{13}C - and ^1H -NMR spectra are consistent with the claimed structure.

EXAMPLE 207

Analogously as described for Example 205 but using 3-(8-chlorosulfonyl-3(RS)-isopropyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester is prepared 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-isopropyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid which is obtained as a white foam after isolation by chromatography on a column of silicagel which is eluted with dichloromethane:methanol (20:1, by vol.). [M+H] = 646.1. The ¹³C- and ¹H-NMR spectra are consistent with the claimed structure.

EXAMPLE 208

Analogously as described for Example 205 but using 3-(8-chlorosulfonyl-3(RS)-butyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester is prepared 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-butyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid. The compound precipitates on acidification (aqueous HCl) of the saponification mixture and, after solution of the precipitate in ethyl acetate, water washing of the solution and drying (MgSO₄) is recovered on evaporation of the solvent as an off-white foam. [M+H] = 659.2. The ¹³C- and ¹H-NMR spectra are consistent with the claimed structure.

EXAMPLE 209

Analogously as described for Example 205 but using 3-(8-chlorosulfonyl-3(RS)-isobutyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester is prepared 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-isobutyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid. The compound precipitates on acidification (aqueous HCl) of the saponification mixture and, after solution of the precipitate in ethyl acetate, water washing of the solution and drying (MgSO₄) is recovered on evaporation of the solvent as a white foam. [M+H] = 659.2. The ¹³C- and ¹H-NMR spectra are consistent with the claimed structure.

EXAMPLE 210

Analogously as described for Example 205 but using 3-(8-chlorosulfonyl-3(RS)-methyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester is prepared 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-methyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid. The compound is extracted after acidification (aqueous HCl) of the saponification mixture with ethyl acetate, and after water washing of the extracted solution and drying (MgSO_4) is recovered on evaporation of the solvent as a white foam. $[M+H] = 617.2$. The ^{13}C - and ^1H -NMR spectra are consistent with the claimed structure.

EXAMPLE 211

Analogously as described for Example 135 but using 6-chloro-8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydroquinoline-5-carboxylic acid methyl ester and 4-(2-fluoro-ethyl)-piperidine hydrochloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride and acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester difluoroacetate is prepared 8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-6-chloro-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-5-carboxylic acid methyl ester which is obtained as a pale yellow gum after purification by chromatography on a column of silicagel using ethyl acetate:hexane (1:1, by vol.) as eluant. The ^{13}C - and ^1H -NMR spectra are consistent with the claimed structure. $[M+H]^+ = 651.9, 653.9$

EXAMPLE 212

Analogously as described for Example 135 but using 8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydroquinoline-5-carboxylic acid methyl ester and 4-(2-fluoro-ethyl)-piperidine hydrochloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride and acetic acid 2-(2-piperazin-1-yl-ethoxy)-ethyl ester difluoroacetate is prepared 8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-5-carboxylic acid methyl ester, isolated as a pale yellow foam after purification by chromatography on a column of silicagel using ethyl acetate:hexane (1:1, by vol.) as eluant. The ^{13}C - and ^1H -NMR spectra are consistent with the claimed structure. $[M+H]^+ = 617.2$.

EXAMPLE 213

8-{2-Benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-5-carboxylic acid methyl ester (31mg) is dissolved in methanol (1ml) and aqueous sodium hydroxide (4M, 0.075ml) is added. The mixture is stirred at 20°C for 9 days, aqueous hydrochloric acid (M, 0.5ml) and water (5ml) are added and the solution is extracted with ethyl acetate (2x5ml). The combined extracts are dried (MgSO₄) and solvent evaporated to give impure material which is purified by chromatography on a column of silicagel using increasing amounts of methanol in ethyl acetate (from 2 to 100%, by vol.). Combination of appropriate fractions gives material which is redissolved in ethyl acetate, filtered and the solution evaporated to give 8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-5-carboxylic acid as a white solid. The ¹H-NMR spectrum is consistent with the claimed structure. [M+H]⁺ = 603.2.

EXAMPLE 214

6-(2-Hydroxy-ethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (125mg) is dissolved in dichloromethane (2ml), cooled to -78°C and DAST (0.03ml) is added. The mixture is allowed to warm to room temperature, diluted with dichloromethane (20ml), washed with saturated aqueous sodium bicarbonate (10ml), dried (MgSO₄) and the solvent evaporated to give a residue which is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (1:1, by vol.) as eluant to give 6-(2-fluoro-ethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a white powder after lyophilisation from aqueous solution. The ¹³C- and ¹H-NMR spectra are consistent with the claimed structure. [M+H]⁺ = 605.4.

EXAMPLE 215

Analogously as described for Example 205 but using 3-(8-chlorosulfonyl-3(RS)-methoxymethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester is prepared 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-methoxymethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid which is obtained pure as a precipitated solid on acidification of the saponification mixture of the ethyl ester precursor. The ^{13}C - and ^1H -NMR spectra are consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 647.4$.

EXAMPLE 216

Analogously as described for Example 205 but using 3-(8-chlorosulfonyl-3,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester in place of 3(RS)-ethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester which, on saponification, affords 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid as a pale yellow solid on evaporation of a solution in dichloromethane. Purification is by chromatography on a column of silicagel using methanol:ethyl acetate (to 3:17, by vol.) as eluant. It has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 645.3$.

EXAMPLE 217

A solution of oxalyl chloride in dichloromethane (2M, 0.34ml) is added to a solution of dimethylsulfoxide (0.047ml) in dichloromethane (1ml) at -78°C . A solution of 3,3-dimethyl-6-(3-hydroxy-propyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (420mg) in dichloromethane (1ml) is added by syringe at -78°C under an atmosphere of nitrogen and the reaction is stirred for 5 minutes at -78°C .

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Triethylamine (0.17ml) is added and the mixture is allowed to warm to room temperature, dichloromethane (5ml) is added and the solution is washed with portions (5ml) of water and aqueous hydrochloric acid (2M), dried (MgSO_4) and the solvent removed by rotary evaporation to give crude 3,3-dimethyl-6-(3-oxo-propyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide which is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:1, by vol.) as eluant. It has a $^1\text{H-NMR}$ spectrum consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 614.24$.

EXAMPLE 218

a) 3,3-Dimethyl-6-(3-oxo-propyl)-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide (300mg) is dissolved in dry dichloromethane (5ml) and cyanotriphenylphosphorane (439mg) is added. The mixture is stirred for 64 hours at room temperature, the solvent removed by rotary evaporation and the pure 6-(4-cyano-but-3-enyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide is isolated by flash chromatography on a column of silicagel using ethyl acetate:hexane (1:1, by vol.) as eluant. It has a $^1\text{H-NMR}$ spectrum consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 638.4$.

b) 6-(4-Cyano-but-3-enyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide (200mg) is dissolved in ethyl acetate (20ml) and hydrogenated (1.35 bar) in the presence of 10% palladium on charcoal (15mg) for 16 hours at 20°C to give 6-(4-cyano-butyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide as a white solid, purified by passage in ether through a small column of silicagel. It has a $^1\text{H-NMR}$ spectrum consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 640.2$.

EXAMPLE 219

6-(4-Cyano-butyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide (150mg) is dissolved in methanol (10ml) and aqueous sodium hydroxide (4M, 4ml) and aqueous hydrogen peroxide (0.58M, 1ml) are added. The solution is stirred for 2 hours at 20°C, the volume is reduced to 5 ml and the solution is acidified (aqueous hydrochloric acid, 2M). The solution is extracted with dichloromethane (2x20ml), the combined extracts dried (MgSO₄) and the solvent removed by rotary evaporation to give crude 5-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-pentanoic acid which is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (95:5, by vol.) as eluant. It has a ¹H-NMR spectrum consistent with the claimed structure. [M+H]⁺ = 658.4.

EXAMPLE 220

3-(8-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid (500mg) and dimethylformamide dimethyl acetal (0.27ml) are suspended in toluene (10ml) and heated for 1 hour at 80°C. Ethyl acetate (25ml) is added to the cooled solution which is extracted with portions (20ml) of aqueous hydrochloric acid (2M, x2), brine, saturated aqueous sodium bicarbonate (x2), dried (MgSO₄) and the solvent removed by rotary evaporation to give crude 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid methyl ester which is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (3:7, by vol.) as eluant. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 645.3.

EXAMPLE 221

a) Analogously as described for Example 205 but starting from 3-[3(RS)-(tert.-butyl-diphenyl-silanyloxymethyl)-8-chlorosulfonyl-1,2,3,4-tetrahydro-quinolin-6-yl]-propionic acid ethyl ester is prepared 3-[8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-(tert.-butyl-diphenyl-silanyloxymethyl)-1,2,3,4-tetrahydro-quinolin-6-yl]-propionic acid ethyl ester which is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (1:1, by vol.) as eluant.

b) 3-[8-{2-Benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-(tert.-butyl-diphenyl-silanyloxymethyl)-1,2,3,4-tetrahydro-quinolin-6-yl]-propionic acid ethyl ester (100mg) is dissolved in dry THF (3ml) and tetrabutylammonium fluoride (60mg) is added. After stirring at room temperature for 8 hours, the solvent is removed by rotary evaporation and the residue obtained is dissolved in ether (5ml). The solution is washed with brine (5ml), dried (MgSO₄) and the solvent removed by rotary evaporation to give 3-[8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-hydroxymethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-propionic acid ethyl ester which is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (1:3, by vol.) as eluant.

c) 3-[8-{2-Benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-hydroxymethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-propionic acid ethyl ester (67mg) is dissolved in methanol (4ml) and aqueous sodium hydroxide (M, 2ml) is added. The mixture is stirred at room temperature for 3 hours, the methanol removed by rotary evaporation and the aqueous solution acidified (aqueous hydrochloric acid, 2M). Ethyl acetate (10ml) is added to dissolve the white precipitate formed and the separated organic phase is washed with water (5ml), dried (MgSO₄) and the solvent removed by rotary evaporation to give 3-[8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-hydroxymethyl-1,2,3,4-tetrahydro-quinolin-6-yl]-propionic acid as a pale yellow foam. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 633.4.

EXAMPLE 222

Analogously as described for Example 110 but using 8-chlorosulfonyl-3,3-diethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester in place of 8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester is prepared 8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-diethyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid ethyl ester. It has ¹H- and ¹³C-NMR spectra consistent with the claimed structure. [M+H]⁺ = 659.5.

EXAMPLE 223

6-(2-Hydroxy-ethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-fluoro-ethyl-piperidin-1-yl]-2-oxo-ethyl}-amide (100mg) is dissolved in dichloromethane (6ml) and Huenig Base (0.039ml) and methoxymethyl chloride (0.026ml) are added. The mixture is stirred for 16 hours at 20°C. Water (5ml) is added and the mixture is extracted with portions (2x10ml) of dichloromethane. The combined extracts are dried (MgSO₄) and solvent removed to give a residue which is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (1:1, by vol.) as eluant to give 6-(2-methoxymethoxy-ethyl)-1-methoxymethyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as an off-white foam. It has a ¹H-NMR spectrum consistent with the claimed structure. [M+H]⁺ = 689.1.

EXAMPLE 224

6-(2-Hydroxy-ethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-fluoro-ethyl-piperidin-1-yl]-2-oxo-ethyl}-amide (100mg) is dissolved in dichloromethane (1ml) and Huenig Base (0.026ml) and methoxymethyl chloride (0.026ml) are added. The mixture is stirred for 4.5 hours at 20°C. Saturated aqueous sodium bicarbonate (5ml) is added and the mixture is extracted with portions (2x10ml) of dichloromethane.

The combined extracts are washed with brine (10ml), dried (MgSO_4) and solvent removed to give an oil which is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (2:3, by vol.) as eluant to give 6-(2-methoxymethoxy-ethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid (2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl)-amide. It has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 647.3$.

EXAMPLE 225

a) 3-(8-{2-Benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-hydroxymethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (100mg) is dissolved in dichloromethane (1ml) and triethylamine (0.025ml) and toluene 4-sulfonyl chloride (35mg) are added. The mixture is stirred for 4 days at 20°C and solvent is removed by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (1:1, by vol.) as eluant to give 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-(toluene-4-sulfonyloxymethyl)-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester.

b) 3-(8-{2-Benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-(toluene-4-sulfonyloxymethyl)-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (100mg) is dissolved in DMF (2ml) and sodium thiomethoxide (17mg) is added. The mixture is stirred for 2 hours at 20°C . Ethyl acetate (10ml) is added and the solution is washed with portions (10ml) of aqueous hydrochloric acid (M) and water, dried (MgSO_4) and the solvent removed by rotary evaporation to give a residue which is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (2:3, by vol.) as eluant to give 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-methylsulfanylmethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a colourless oil.

c) 3-(8-{2-Benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-methylsulfanylmethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (75mg) is dissolved in methanol (1.5ml) and aqueous sodium hydroxide (M, 1.5ml) is added. The mixture is stirred for 3 hours at 20°C .

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The methanol is removed by rotary evaporation and the aqueous solution acidified with aqueous hydrochloric acid (2M). The suspension is extracted with portions (2x5ml) of ethyl acetate and the combined extracts are dried (MgSO_4) to give 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-methylsulfanylmethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid as a white foam. It has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 663.2$

EXAMPLE 226

a) 3-(8-{2-Benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-(toluene-4-sulfonyloxymethyl)-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (125mg) is dissolved in DMF (2ml) and Huenig Base (0.053ml) and a solution of dimethylamine in THF (2M, 0.306ml) are added. The mixture is stirred for 3 days at 45°C . Ethyl acetate (10ml) is added to the cooled solution and the mixture is extracted with water (10ml), dried (MgSO_4) and solvent removed by rotary evaporation to give a residue which is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (20:1, by vol.) as eluant to give 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-dimethylaminomethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a colourless oil. It has a ^1H -NMR spectrum consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 688.5$

b) 3-(8-{2-Benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-dimethylaminomethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (81mg) is saponified as described for Example 225c. Extraction of the reaction mixture by dichloromethane affords 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3(RS)-dimethylaminomethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid as a white solid. It has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 660.3$.

EXAMPLE 227

3-(8-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid (300mg) is suspended in propan-1-ol (10ml) and dry hydrogen chloride gas is passed through the solution for 1 minute. The solution is poured into saturated aqueous sodium bicarbonate (100ml) and the mixture is extracted with portions (2x50ml) of ethyl acetate. The combined extracts are dried (MgSO_4) and evaporated to give 3-(8-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid propyl ester which is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (7:3, by vol.) as eluant. It has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 673.4$.

EXAMPLE 228

a) 3-(8-{2-Benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-3,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (64mg) is dissolved in ethanol (4ml) and the solution is cooled to 5°C . Sodium borohydride (9mg) is added and the mixture is stirred at 5°C for 48 hours. Further portions (9mg and 5mg) of sodium borohydride are added at intervals (1 hour and 3.5 hours, respectively) and water (5ml) is added. After stirring for 15 minutes, ethyl acetate (20ml) is added and the recovered organic phase is washed with brine (10ml), dried (MgSO_4) and the solvent removed by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using dichloromethane:ethyl acetate (3:2, by vol.) as eluant to give 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-4(RS)-hydroxy-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester as a colourless gum.

b) 3-(8-{2-Benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-4(RS)-hydroxy-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester (80mg) is saponified as described for Example 225c to afford 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-4(RS)-hydroxy-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid as a colourless foam. It has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 674.3$.

EXAMPLE 229

Analogously as described for Example 205 but using 3-(8-chlorosulfonyl-3(RS)-ethoxy-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester in place of (8-chlorosulfonyl-3(RS)-ethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester is prepared 3-(8-(2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl)-3(RS)-ethoxy-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid. It is obtained as a white foam which has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 647.4$.

EXAMPLE 230

Analogously as described for Example 164 but using 6-[2-(tert.-butyl-diphenyl-silanyloxy)-ethyl]-3,3-diethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 6-[2-(tert.-butyl-diphenyl-silanyloxy)-ethyl]-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 6-(2-hydroxy-ethyl)-3,3-diethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. After purification by flash chromatography on a column of silicagel eluted with ethyl acetate:hexane (2:1, by vol.) it is obtained as an amorphous solid which has ^1H - and ^{13}C -NMR spectra consistent with the claimed structure. $[\text{M}+\text{H}]^+ = 631.5$.

EXAMPLE 231

Analogously as described for Example 129 but using 1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride is prepared 1,2,3,4-tetrahydro-quinoline-8-sulfonic acid {2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide. The product is obtained as a white foam after purification by flash chromatography on a column of silicagel eluted with ethyl acetate:dichloromethane (1:3, by vol.) and evaporation of a solution of the product from dichloromethane. $[\text{M}+\text{H}]^+ = 531.3$. The ^1H - and ^{13}C -NMR spectra are consistent with the claimed structure.

EXAMPLE 232

Analogously as described for Example 161 but using 8-chlorosulfonyl-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-6-propionic acid ethyl ester in place of 3,3-dimethyl-1,2,3,4-tetrahydro-quinoline-8-sulfonyl chloride and 4-(2-fluoro-ethyl)-piperidine hydrochloride in place of 1-(2-fluoro-ethyl)-piperazine hydrochloride is prepared 3-(8-{1(R)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl-sulfamoyl}-3,3-dimethyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester which is saponified as described for Example 109c to give the corresponding acid which is obtained as a white solid. $[M+H]^+ = 631.3$. The 1H - and ^{13}C -NMR spectra are consistent with the claimed structure.

EXAMPLE 233

Analogously as described for Example 205 but using 3-(8-chlorosulfonyl-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid ethyl ester is prepared 3-(8-{2-benzothiazol-2-yl-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethylsulfamoyl}-1,2,3,4-tetrahydro-quinolin-6-yl)-propionic acid which is obtained as a white foam. $[M+H]^+ = 603.2$. The 1H - and ^{13}C -NMR spectra are consistent with the claimed structure.

EXAMPLE 234

Determination of the potency of the compounds.

The compounds are analysed for their effect on the human α -thrombin-catalysed hydrolysis of the substrate Kabi S-2238 (Kabi Vitrum (UK) Ltd). The K_m and K_p values are derived from a Lineweaver-Burk plot of data, from which is calculated the K_i value for the inhibitors. The potency of compounds with respect to human α -thrombin is expressed as their kinetic inhibition constant (K_i), and into the second series was added an equivalent volume of the vehicle alone. The reactions were started by the addition of human α -thrombin (Sigma, T-8885) to give a final activity of 0.0625 NIH units/ml. Following mixing by inversion, the initial reaction rate (as change in absorbance per minute) was measured using a Perkin Elmer Lambda 5 spectrophotometer (fitted with a cuvette holder thermostatted at 37°C) at 405nm over a period of 1 minute during which time the rate was linear and showing no signs of substrate depletion.

Duplicate series of reaction mixtures are prepared comprising chromogenic substrate S-2238 (Kabi Vitrum) in Tris/HCl buffer (0.05M, pH 8.4) with a range of concentrations of substrate from 3.125 μ M to 100 μ M. The solutions are brought to 37°C in a thermostatically regulated heating block. Into one of the sets of duplicates is added inhibitor dissolved in a compatible vehicle (water, methanol or DMSO) to give a final concentration close to the expected K_i , and into the second series was added an equivalent volume of the vehicle alone. The reactions are started by the addition of human α -thrombin (Sigma, T-8885) to give a final activity of 0.0625 NIH units/ml. Following mixing by inversion, the initial reaction rate (as change in absorbance per minute) is measured using a Perkin Elmer Lambda 5 spectrophotometer (fitted with a cuvette holder thermostatted at 37°C) at 405nm over a period of 1 minute during which time the rate is linear showing no signs of substrate depletion.

Table Potency (K_i) of Examples expressed in μ Moles

Example	K_i	Example	K_i	Example	K_i
4	0.033	8	0.018	10	0.023
20	0.036	27	0.046	38	0.034
40	0.034	55	0.031	56	0.011
57	0.046	60	0.011	58	0.026
75	0.019	76	0.020	77	0.020
80	0.007	81	0.006	82	0.012
83	0.007	85	0.043	87	0.020
96	0.126	113a	0.080	116	0.101
126	0.049	129	0.026	164	0.045
166	0.047	195	0.056	197	0.043
198	0.023	199	0.045	200	0.064
202	0.070	203	0.094	204	0.027
212	0.084	224	0.084	225	0.094
230	0.049				

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Using active substances as described in any of the foregoing Examples, the following dosage forms are made.

EXAMPLE 235

Tablets suitable for oral administration.

Tablets containing the ingredients indicated below may be prepared by conventional techniques.

Amount per Tablet	
Ingredient	(mg)
Active substance	250
Lactose	140
Corn starch	35
Talcum	20
Magnesium stearate	5
Total	<hr/> 450 mg <hr/>

EXAMPLE 236

Capsules for oral administration

Capsules of the below are made up by thoroughly mixing together batches of the ingredients and filling hard gelatin capsules with the mixture

Amount per Tablet	
Ingredient	(mg)
Active substance	250
Lactose	250
Total	<hr/> 500 mg <hr/>

EXAMPLE 237

The following ingredients are dissolved in water for intravenous perfusion and the resulting solution is then sterilized

Amount per Tablet

Ingredient	(mg)
Active substance	0.25
Buffer system	as desired
Glucose	25
Distilled water	500

Claims

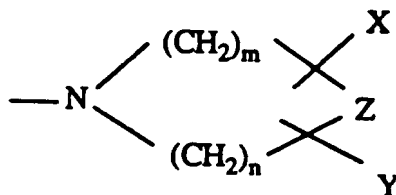
1. A compound of the general formula I



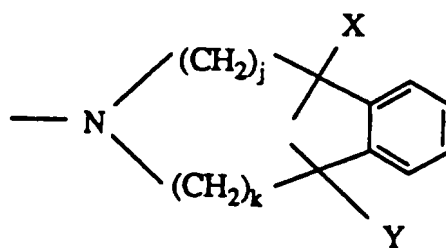
in which Ar is a substituted or unsubstituted aryl or heterocyclic residue; Aa is an amino acid residue and



is a residue of formula IV or formula V



(IV)

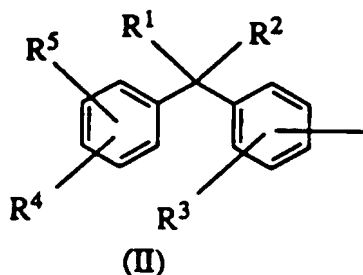


(V)

wherein X is hydrogen or a C₁-C₅ alkyl group, Y is a) a SO₃H, PO(OR¹⁴)₂, OH, SH, NR¹⁵R¹⁶, or halogen group or is b) a residue -(C_qH_{2q})-Q wherein Q is H, COR¹⁴, CO₂R¹⁴, CONR¹⁵R¹⁶, SO₃H, OR¹⁴, OCOR¹⁴, PO(OR¹⁴)₂, NR¹⁵R¹⁶, SR¹⁴ or Hal wherein R¹⁴, R¹⁵ and R¹⁶ are hydrogen, C₁-C₅ alkyl, C₅-C₈ cycloalkyl or C₇-C₁₁ aralkyl or R¹⁵ and R¹⁶ together with the nitrogen atom to which they are bound form a 5 or 6 membered azacycloalkyl or oxazacycloalkyl, q is 0 or an integer from 1 to 8 and the residue C_qH_{2q} may be optionally substituted by OH or interrupted by

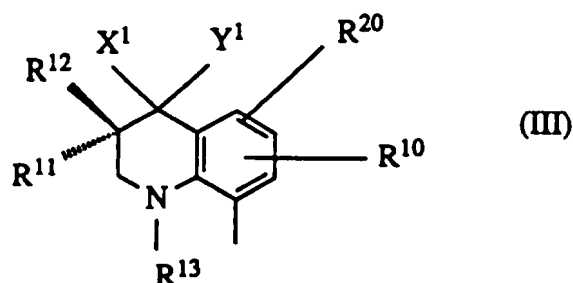
oxygen, sulfur, oxycarbonyl O.CO, carbonyloxy CO.O, aminocarbonyl NHCO, sulfonamido, NHSO_2 or carboxamido CONH; or is c) a residue $(\text{C}_w\text{H}_{2w+1-y-z})\text{F}_y\text{OH}_z$ in which w is an integer from 1 to 8, y is an integer from 1 to 17 and z is 0 or 1, or X and Y together are = O, Z is a direct bond, oxygen or nitrogen optionally substituted by X or Y, m = 2 to 4, n = 2 to 4 and m+n = 4 to 6, j = 0 to 2, k = 0 to 2 and j+k = 2 or 3 wherein X has its previous significance and Y is a residue $(\text{C}_q\text{H}_{2q})\text{-Q}$ wherein q and Q have their previous significance, and salts thereof, provided that when Aa is arginine X and Y are not alkyl and when Q is COR^{14} , q is an integer from 1 to 8.

2. A compound as claimed in claim 1 in which Ar is a substituted or unsubstituted phenyl residue, a substituted or unsubstituted naphthyl or partially hydrogenated naphthyl residue or a substituted or unsubstituted anthryl, phenanthryl or heterocyclic residue which may be partially hydrogenated.
3. A compound as claimed in claim 1 or 2 in which Ar is a residue of formula II



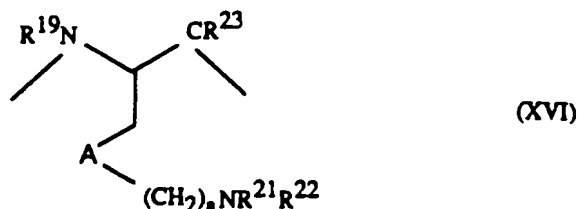
wherein R^1 and R^2 are $\text{C}_1\text{-C}_5$ alkyl or are linked to form a $\text{C}_3\text{-C}_7$ carbocyclic ring and R^3 , R^4 and R^5 are the same or different and are hydrogen, $\text{C}_1\text{-C}_5$ alkyl, OR^6 , SR^6 , halo, NR^7R^8 , NO_2 , CN, CONR^7R^8 or CO_2R^9 wherein R^6 is $\text{C}_1\text{-C}_5$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, $\text{C}_7\text{-C}_{11}$ aralkyl and R^7 , R^8 , and R^9 are hydrogen, $\text{C}_1\text{-C}_5$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, or $\text{C}_7\text{-C}_{11}$ aralkyl, or R^7 and R^8 together with the nitrogen atom to which they are bound form a 5 or 6 membered azacycloalkyl or oxazacycloalkyl.

4. A compound as claimed in claim 3 in which R^3 is H or NH_2 and R^4 and R^5 are H or OCH_3 .
5. A compound as claimed in claim 1 in which Ar is a residue of formula III,

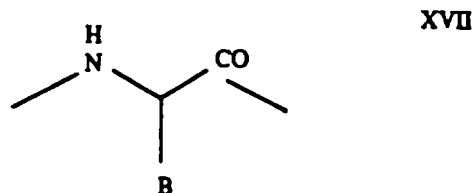


wherein R^{10} is hydrogen, halo e.g. bromo, chloro or fluoro, R^{20} is hydrogen or $(CH_2)_pD$ where p is 0 or an integer from 1 to 4 and D is C_1 - C_5 alkyl optionally interrupted by one or more oxygen atoms, C_1 - C_5 alkenyl, C_1 - C_5 alkoxy, a silane group, CHO, tetrazolyl, carboxyl, alkylcarboxyl, fluoro, cyano or CHNOH, R^{11} and R^{12} are hydrogen, a C_1 - C_5 alkyl which may be interrupted by one or more oxygen atoms, C_1 - C_5 alkenyl, alkoxyalkyl, hydroxyalkyl, alkylthioalkyl, alkylamino dialkylamino or trialkylamino, or together form either a methylene group or together with the carbon to which they are attached form a C_3 - C_7 carbocyclic ring, and R^{13} is hydrogen, C_1 - C_5 alkyl which may be interrupted by one or more oxygen atoms or C_7 - C_{11} aralkyl and X^1 and Y^1 are both H, one is H and one is OH or together are = O.

6. A compound as claimed in claim 5 in which most preferred are those compounds of formula I wherein Ar is a residue of formula III wherein.
7. A compound as claimed in any preceding claim in which amino acid residue Aa is a heteroaliphatic or heteroaromatic group having the formula XVI



where R^{19} is H or CH_3 , R^{23} is = O or = S, A is O, S, NH, SO_2 , CH_2S or CH_2 , R^{21} is H or CH_3 , R^{22} is H or CH_3 or when R^{21} is H may also be $C(NH_2) = NH$, and a is an integer from 1 to 4 or the formula XVII



where B is a heterocyclic ring or heterocyclic methyl group, wherein the heterocyclic ring is optionally fused to a second ring which is a hydrocarbon or heterocyclic ring, and wherein the single or double ring system is optionally substituted by methyl, aminomethyl, phenyl or OH.

8. A compound as claimed in any preceding claim in which



represents a piperidine group of formula IV as defined in claim 1.

9. A compound as claimed in claim 8 in which the piperidine ring is substituted by an ethyl group or a fluoroethyl group.
10. A compound of the formula I as claimed in claim 1 in which Ar has the formula III as defined in claim 5, Aa has the formula XVI as defined in claim 7 and



has the formula IV as defined in claim 1 or 9.

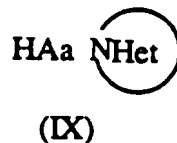
11. A compound of the formula I as claimed in claim 1 in which Ar has the formula III as defined in claim 5, Aa has the formula XVII as defined in claim 7 and



has the formula IV as defined in claim 1 or 9.

12. A compound as claimed in any preceding claim in which amino acid residue Aa is of L configuration.

13. A process for preparing a compound as claimed in any preceding claim which comprises the reaction of an amino acyl amide of formula IX,



wherein Aa and



are as defined in any one of claims 1, 7 to 9 and 12 with an arylsulfonic acid derivative of formula VIII



where W is OH or preferably an arylsulfonyl halide VIII where W is halogen especially Cl or Br and where the compounds of formula IX and VIII may be optionally protected and/or where the residue ArSO_2 in compounds of formula I comprises a partially hydrogenated aromatic or heterocyclic system the compounds of formula VIII may contain hydrogenatable double bonds.

14. A process as claimed in claim 13 in which the compound of formula IX is prepared by reaction of an amino acid with a nitrogen heterocycle of formula VII

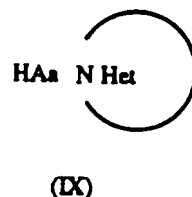


wherein



is as defined in any one of claims 1, 7 to 9 and 12 and where the amino acid and the compound of formula VII is optionally protected.

15. A compound of formula IX



wherein Aa and



are as defined in any one of claims 1, 7 to 9 and 12.

16. A process for preparing a compound as claimed in any one of claims 1 to 12 which comprises the reaction of an arylsulfonyl amino acid compound of formula VI,



in which Ar is as defined in any one of claims 1 to 5 and Aa is as defined in claim 1, 7 or 12 with a nitrogen heterocycle of formula VII



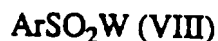
wherein



is as defined in any

one of claims 1, 8 or 9 and where the compounds of formulae VI and VII are optionally protected.

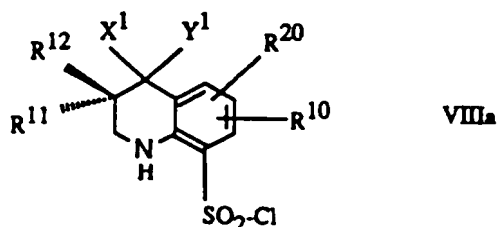
17. A process as claimed in claim 16 in which the compound of formula VI is prepared by reacting an amino acid, which may be optionally protected, with an aryl sulfonic acid derivative of formula VIII



where W is OH or halogen in the presence of a base.

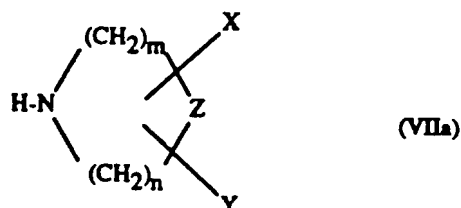
18. A compound of formula VI as defined in claim 16.

19. A Compound of formula VIIIa



where $R^{11} = R^{12} =$ methyl or ethyl; $R^{11} =$ hydrogen and $R^{12} =$ methyl; $R^{11} =$ methyl and $R^{12} =$ hydrogen; or where one of R^{11} and R^{12} is hydrogen and the other is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or sec-butyl (other than the RS monomethyl compound) and X^1 and Y^1 are both H, one is H and one is OH or together are = O.

20. A compound of formula VIIa



in which X is hydrogen or C_1 - C_5 alkyl;
Y is $(C_q H_{2q})-Q$ or $(C_w H_{2w+1-y-z})F_y OH_z$ where Q is COR^{14} , CO_2R^{14} , $CONR^{15}R^{16}$, SO_3H , OR^{14} , $OCOR^{14}$, $PO(OR^{14})_2$, $NR^{15}R^{16}$, SR^{14} or halogen wherein R^{14} , R^{15} and R^{16} are independently hydrogen C_1 - C_5 alkyl, C_5 - C_8 cycloalkyl or C_7 - C_{11} aralkyl groups, or R^{15} and R^{16} together with the nitrogen atom to which they are bound form a 5 or 6 membered azacycloalkyl or oxazacycloalkyl, q is 0 or an integer from 1 to 8, w is an integer from 1 to 8, y is an integer from 1 to 17 and z is 0 or 1 and the residue $C_q H_{2q}$ may be optionally substituted by OH or interrupted by oxygen, sulfur, oxycarbonyl O.CO, carbonyloxy CO.O, aminocarbonyl NHCO, sulfonamido, $NHSO_2$ or carboxamido CONH, Z is a direct bond, oxygen or nitrogen optionally substituted by X or Y, m is an integer from 2 to 4, n is an integer from 2 to 4 and $m + n$ is 4 to 6 providing that when Q is a group COR^{14} , CO_2R^{14} , $CONR^{15}R^{16}$, SO_3H , OR^{14} , $NR^{15}R^{16}$ or SR^{14} , or when Q is a group O. COR^{14} and Z is nitrogen, and q is not 1 and if q is 2 to 4 then the residue $C_q H_{2q}$ is interrupted by oxygen sulfur, oxycarbonyl O.CO, carboxyloxy CO.O, aminocarbonyl NHCO, or carbamoyl CONH.

providing that when Q is a group COR^{20} , CO_2R^{20} , $\text{CONR}^{20}\text{R}^{21}$, SO_3H , OR^{20} , $\text{NR}^{20}\text{R}^{21}$ or SR^{20} , or when Q is a group O.COR^{20} and Z is nitrogen, and q is not 1 and if q is 2 to 4 then the residue C_qH_{2q} is interrupted by oxygen sulfur, oxycarbonyl O.CO , carboxyloxy CO.O , aminocarbonyl NHCO , or carbamoyl CONH .

21. A pharmaceutical composition which comprises a compound of formula I as defined in any one of claims 1 to 12 and a pharmaceutically acceptable carrier or diluent.
22. A compound as claimed in claim 1 substantially as hereinbefore described with reference to any one of the foregoing Examples.

INTERNATIONAL SEARCH REPORT

Inter national Application No
PCT/GB 96/00520

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/12 C07D211/62 A61K31/445 A61K31/47 C07D211/20
C07D295/18 C07D215/36 C07D211/22 C08K5/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K C08K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 22344 (CIBA-GEIGY AG) 11 November 1993	1-4,7,8,
Y	see examples 2,10,11-13 and formula XII on page 8	12,15
	see the whole document	1-22

X	PROG. FIBRINOLYSIS, vol. 6, 1983, pages 315-317, XP002005157	1,2,5-8
	S.OKAMOTO ET AL: "Similarity and dissimilarity of stereogeometry of active center of plasmin and thrombin"	
Y	see the whole document	1-22

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

10 June 1996

Date of mailing of the international search report

31.07.96

Name and mailing address of the ISA

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Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 96/00520

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 10, no. 4 (C-322), 9 January 1986 & JP,A,60 163815 (MITSUBISHI KASEI KOGYO KK), 26 August 1985, compound RN 102125-53-1, piperidinecarboxamide,1-[5-[(aminoiminomet hyl)amino]-1-oxo ---	1,2,5-8
X	EP,A,0 008 746 (MITSUBISHI CHEMICAL INDUSTRIES LTD) 19 March 1980 see the whole document, especially examples and the formula IV on page 6 ---	1,2,5-8, 10,11,20
Y	US,A,5 371 091 (BRISTOL-MYERS SQUIBB CO.) 6 December 1994 see the whole document ---	1-22
Y	EP,A,0 555 824 (DR KARL THOMAE GMBH) 18 August 1993 see the whole document ---	1-22
X	EP,A,0 565 396 (SYNTHELABO) 13 October 1993 Y see formula IX see the whole document -----	20 1-22

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB96/00520

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please see attached sheet ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The use of the terms Ar, Aa and the definition of N Het are so broad that a meaningful search is not possible. The provisos are ambiguous, and the exclusion only of Q=0 when Q is COR¹⁴ does not include argatroban and its derivatives. The intermediate claims 15, 18 and 20 are not fully searchable, due to the definitions of N Het and Aa. The claim 20 disclaimer is unclear

Claims searched completely: 7 (when dependent on 3 or 5), 10, 11, 19

Claims searched incompletely: 1 - 6, 7 when dependent on 1, 8, 9, 12 - 18, 20, 21 and 22

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 96/00520

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